PATIENT PERSPECTIVES OF PARTICIPATION IN A RANDOMISED CONTROLLED TRIAL

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ABSTRACT

Objectives

To explore trial participants' and non-participants' perspectives of a randomised controlled trial. Principally these patients' understanding of randomisation, their recall and understanding of information about the trial, plus an examination of their expectations and preferences.

Design

This exploratory study is concerned with re-focusing onto the patients' experience, therefore qualitative in-depth, semi-structured interviews were carried out with 22 participants and 11 non-participants who were eligible to participate in the ClasP randomised controlled trial. Interviews were recorded on audio tape and fully transcribed. Data were analysed by comparing transcripts and describing emergent themes, using a grounded theory approach. Case studies were also carried out for each respondent.

Setting

The CLasP study comprises three linked pragmatic RCTs to evaluate the effectiveness and cost effectiveness of a new technology (laser therapy - ELAP) compared with standard surgery (transurethral resection of the prostate - TURP) for men with evidence of acute or chronic retention of urine who require active intervention, and laser, TURP and conservative management (monitoring without active intervention) for men with lower urinary tract symptoms related to benign prostatic disease.

Subjects

The study reported here sets out to elicit the perspectives of 'ordinary' middle-aged and elderly men who require elective treatment for a common condition, and have either agreed or refused to participate in a pragmatic randomised controlled trial.

Purposeful sampling was used to include eligible patients who had decided not to participate in the trial from each of the main reasons as reported in the trial records. Trial participants were also interviewed from both trial centres, and included a number who had been allocated to each of the treatment arms at different stages of trial participation and receiving different treatments within the trial.

Interventions and outcome measures

Interviews used a checklist of topics to encourage participants to describe their experiences. Narratives concerning their their recall and understanding of information about the trial, their expectations and preferences were compared to identify common themes, retaining the context of the discussion to allow detailed interpretation. Case studies were used to examine the dialogue that participants engaged in a to try and make sense of the trial design, their lay beliefs and their actual experiences of participation or non-participation.

Results

It was found that the majority of the participants were aware of some aspects of randomisation and most (15/22) acknowledged the involvement of chance in their allocation. A large number of the non-participants were also aware of some aspects of randomisation and almost all (9) could recall that the trial was some sort of experiment. However, their recall was at a lower level than that of the participants and only a small number (4/11) were aware of the involvement of chance.

All but one (Mr Taylor) of the trial participants also held other co-existing ideas about non-randomised methods of allocation such as rationing and individualised treatment, which they used to understand and explain their treatment allocation. For a small number, altruism (7) and an expectation of personal benefits (7) were motivations for taking part. However, trust (10), distrust (11) and their beliefs about fate and destiny (13) developed as they tried to make sense of their treatment allocation in relation to their treatment preferences.

Surprisingly, the non-participants made sense of their experience of being asked to participate in similar ways. Some placed their trust in the clinician, believing they received the best treatment by receiving individualised care (see Mr Young). For some this was thought to be within the trial and thus cynically believed that they had been excluded from the trial and that the most effective treatment was being rationed and denied them (see Mr McCarthy).

Three main types of refusal were identified: those who made an active decision not to take part in the trial (5), those who believed that they had agreed to participate (3), and those having no recall of being invited to participate in the trial (3). Surprisingly a small number of non-participants also appeared willing to participate in the trial, citing trust (7), personal benefits (4) and altruism (2) as motivations. Half of these patients (6) expressed anxiety about their treatment and may be why they are 'refusers'.

The key to understanding peoples' experiences of RCTs lies in the basic inconsistencies of trial design, as shown in these mens' struggle to piece together what paricipation means. Each individual's narrative about trial participation was analysed as a case study and this showed that most participants engaged in a dialogue to try and make sense of the trial design, their lay beliefs and their actual experiences of participation.

Conclusions

This study confirms the importance of providing clear and accurate patient information, but also shows that this in itself is unlikely to ensure consistent interpretation of concepts such as randomisation by participants. The patient information in this study was well received and largely accurately recalled, but patients still struggled with the concepts underlying the design and developed sometimes competing accounts. It may be that participants need to discuss the reasons for particular methods of trial design (such as randomisation) with researchers and reflect on these in order to understand them fully enough to give true informed consent.

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AUTHOR'S DECLARATION

I declare that this thesis is based on the original work of the author. Full reference has been made to published sources used, and all advice and assistance received has been acknowledged. The views expressed in this thesis are my own and not necessarily those of the University. This thesis has not been previously presented for degree in this or any other university.

All aspects of the design and execution of the research were undertaken by myself, with guidance from my PhD advisor.

Some of the material contained within this thesis has previously been published in the following paper:

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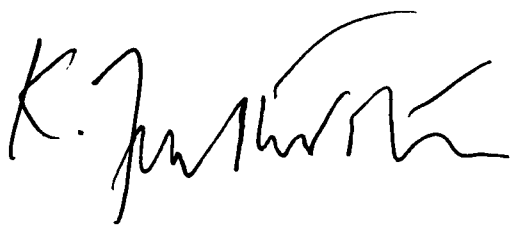
Signed:  Date: 14/06/00

Summary of the research findings

Patients' expectations of and experiences of participating in randomised controlled trials

There is an increasing reliance on the randomised controlled trial - often regarded as the 'gold standard' in clinical research. The ethical and methodological issues of clinical trials continue to be debated. However the patients' perspective of the process has received little attention, except in trials of rare conditions, or attitudes towards hypothetical trials. This research has focused on thirty middle aged and elderly men involved in a randomised controlled trial of treatments for benign prostatic disease. Twenty participants, purposefully sampled in each of the clinical centres, different treatment arms and at different time points in the trial, were interviewed. In addition, 10 men who refused to participate in the trial were also interviewed. These data were supplemented by participant observation of recruitment.

Data were collected by in-depth interviews carried out by KF using a semi-structured checklist of topics, covering the same basic issues, including initial symptoms; recall, understanding and experience of recruitment; feelings about participation; experiences of treatment and outcome. The aim was to encourage the men to relate stories about their experiences and to explore their understandings of what had happened. Interviews were conducted in the men's homes, audio-tape recorded and lasted from half-an-hour to one-and-a-half-hours. The data were analysed to allow the development of grounded theory.

Among refusers, differences were observed between the reason for not taking part as recorded in notes and the respondents' explanation/interpretation of what took place. It was apparent that for many respondents, the lack of direction from the clinician about the treatments and trial participation was problematic. Among participants, it was clear that while the majority were able to recall aspects of randomisation, many struggled with the concept and developed co-existing alternative accounts to explain treatment allocation. Common terms

used by trialists were often interpreted differently by patients – even apparently simple terms such as 'random' and 'trial.'

It is not clear, however, whether this greater understanding would lead to higher or lower levels of accrual to trials, but such an investigation could be linked with research attempting to incorporate patient preferences into RCTs.

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Introduction

This chapter will summarise the history of the RCT to examine its ascendancy as the 'gold standard' and to place it within the context of other developments in the evaluation of treatments. Considerable debate has focussed on the ethics involved in RCTs and these issues are also considered within this chapter.

The history of the randomised controlled trial

Just over fifty years ago the first randomised controlled trial, the MRC streptomycin trial of pulmonary tuberculosis[1] was reported. By comparing streptomycin (a new antibiotic) plus bed rest with bed rest alone for the treatment of pulmonary tuberculosis, the trial found that streptomycin was effective.[1] Prior to this trial, there had been a long practice within medical research of comparing treatment groups, where alternate cases were allocated to a treatment at accrual, one of which would receive the intervention and the other acting as a control.[2] The editorial published to coincide with the streptomycin trial report distinguished the method used from such previous practice and emphasised that random allocation, through the "ingenious system of sealed envelopes" (p.792), would ensure that this "removed personal responsibility from the clinician" (p.792) while also eliminating bias in recruiting patients.[3]

Randomisation was used within this trial for two main reasons. First, in response to the limited supplies of streptomycin, randomisation meant that only one half of patients received the active drug. Second, Bradford Hill had been strongly promoting the methodological benefits of randomisation.[2] He argued that the aim of the experimental design must be to "ensure that, as far as possible, the

control and treated groups are the same in all *relevant* respects" (p.42).[4] As Yoshioka points out, the justification for this initial use of randomisation has changed over time. Most contemporary accounts refer to the shortage of streptomycin as the impetus because it meant it was ethically permissible for some patients not to receive this new treatment.[2] More recently, the methodological benefits of randomisation have been advocated.

The MRC trial was not the first to consider new approaches to the elimination of bias and the field of tuberculosis research has played an important role in the methodological development of the randomised controlled trial.[2] Because pulmonary tuberculosis was a varied and unpredictable condition, with bed rest alone leading to recovery in some cases, the assessment of treatments for this condition was difficult. Four years before the MRC trial, in 1944, Hinshaw and Feldman, tuberculosis researchers in the US, set out a number of methodological techniques that could reduce bias, such as setting clear eligibility criteria in order to obtain a comparable group of patients, blinded evaluation and patient allocation to a treatment based on 'some procedure of chance'.[5] In 1931, Amberson et al had similarly advocated the use of controls in the evaluation of the effectiveness of a popular treatment, sanocrysin, which was a gold compound for pulmonary tuberculosis. Twenty-four patients were paired according to age and severity of disease and divided between two groups, with the "flip of the coin" (p.404) allocating the groups to either injections of sanocrysin or distilled water. The researchers found that the control group had a better outcome.[6]

The MRC streptomycin trial of pulmonary tuberculosis is not as novel an approach as it has been portrayed. As Doll points out, the MRC Whooping-cough vaccination trial[7] was the first trial to randomly allocate patients to an intervention, although it was reported later than the streptomycin trial.[8] Moreover, Hrobjartsson et al[9] in a recent paper argue that Fibiger carried out the first clinical trial using randomisation in 1898 in Denmark. Fibiger[10] allocated patients with diphtheria to receive standard treatment or standard treatment

plus injections of diphtheria serum twice daily. Treatment allocation was dependent upon day of admittance using alternate days, thus creating two comparable groups,[10] using a "quasirandomised trial" (p.1245) design.[9] Fibiger was aware of the need to control for selection biases and is noted for the clarity of the reporting of his methods.[9, 11]

Nevertheless, the MRC streptomycin trial was the first to describe the method of random allocation explicitly,[2, 11] even though, as Yoshioka points out, random allocation was scarcely mentioned within the MRC documents relating to the trial at the time.[2] Random allocation was carried out by Bradford Hill, who drew up random sampling numbers for each gender within each centre, the details of which were unknown to any of the investigators or to the co-ordinator. The central office allocated eligible patients by opening the appropriate numbered envelope that assigned them to either streptomycin and bed rest or bed rest alone. The clinician at the treatment centre was then notified.[1] The accompanying editorial highlights the fact that this method attained similar levels of disease between the two groups at baseline.[3]

The streptomycin trial also employed a rigorous approach to other aspects of the trial protocol to avoid bias.[2] The participants and assessors were blinded and the patients were not informed that they would be receiving a different treatment. The trial examined one type of tuberculosis, using narrow eligibility criteria. To ensure standardisation of data collection, each of the participating hospitals recorded patient details on standard forms and carried out examinations at fixed intervals. The data were examined centrally and to avoid bias, the radiological pictures, one of the main outcome measures, were assessed blind by an independent panel of two radiographers and a clinician.[1]

The number of randomised controlled trials since then has mushroomed, becoming a global institution within health care. This development can be seen in the context of other significant scientific advances which are a culmination of processes that occur over a number of years.[8] Yoshioka similarly concludes that "the innovation of centrally controlled randomisation can be attributed to a

combination of scientific logic and political and social pressures on the medical bureaucracy" (p.1223).[2] However, the adoption of randomisation was not straightforward and as Doll points out it was a number of years before randomisation was an accepted element of clinical research.[8]

The RCT is now widely recognised as the 'gold standard' within clinical research, the most effective method to minimise bias and provide valid answers to important clinical questions.[12] The RCT sets out to measure and compare outcomes, that is, the events that are present or absent after trial participants have received an intervention.[13] A trial usually includes an active intervention and a control treatment as part of the experiment. The experimental treatment can, for example be a new drug or procedure, whilst the control is the intervention which is regarded as the standard for comparison, for example the standard practice, a placebo or no intervention.[13] The results of such trials are then used to make inferences about the effectiveness of interventions within the whole population. Cochrane predicted that the implementation of such research could lead to "an increased effectiveness and efficiency. There will be a marked reduction in the use of ineffective remedies and of effective remedies used inefficiently" (p.84).[14]

Since this first trial, the development of the RCT has developed into many different designs and in recent years there has been a proliferation of 'how to' publications.[13, 15-18] The choice of trial design is dependent upon a number of factors, including the aspect of an intervention trialists wish to examine, the method of providing the intervention, patient preferences, sample size and whether the trial should be blinded.[13] Explanatory and pragmatic trials, efficacy and effectiveness trials and phase I, II and III trials all evaluate different aspects of an intervention. The parallel, crossover and factoral trial designs are related to the method of exposure of participants to the trial intervention. Trials also differ in size, from N=1 up to mega-trials which can be fixed or flexible (sequential trials).[13] Future developments include the move towards such 'mega trials',[12, 13]

simple, pragmatic trials which examine large samples of patients and employ a limited number of outcome measures.[13]

However, there is also an increasing awareness of the problems associated with the RCT,[19] including attaining the required level of precision, validity and interpretation. Some suggest that the focus on this method has led to 'randomised trialomania' that has limited clinical research.[20] Other approaches have been suggested, for example the use of retrospective controls and 'computrials'.[19] Future challenges include the examination of disease from the patient's perspective,[21] detecting small but important effects, for example where outcome is qualitative rather than quantitative, and the development of trial designs which take patient preferences into account.[22-24] Trial methods will be considered further in chapter 2.

Considerable debate has also focussed on the ethics involved in RCTs, and these issues are considered in the section that follows.

The ethics of the randomised controlled trial

Introduction

Clinical research is regulated to protect participants from any potential physical harm. It is possible for patients' rights to be violated and in the past, some have received actual physical harm as a result of taking part in clinical research, for example the Holmesburg prisoners.[25, 26] Here, inmates in the Holmesburg prison were paid to take part in dermatology experiments. Although these treatments often appeared to be benign such as shampoo, they often involved painful biopsies. Retin-A was developed in this way. Other experiments involved psychoactive drugs, radioactive isotopes and dioxin. The experiments ended in 1974, however, this remains a contemporary issue. There are on-going exposés of past and current breeches of ethical guidelines, as highlighted by the recent inquiry into the North Staffordshire paediatric ventilation trial. This was set up in response to parents' claims that they were unaware of the experimental nature

of the treatment and had been misled into signing the consent form for a trial comparing a new type of ventilator with conventional treatment for premature babies.[27, 28]

In response to the Nuremburg trial of Second World War medical atrocities, the Nuremberg Code of 1947 sets out a number of principles to protect research participants. This states that consent must be voluntary and free from "constraint or coercion" and that participants must be able to choose not to continue with the experiment. The researcher has a personal duty to ensure the quality of such consent and that participants have "sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him (sic) to make an understanding and enlightened decision".[29]

The Nuremberg Code also indicated that experiments must not be "random or unnecessary" with the design based either on the results of animal experiments or knowledge of the natural history of the condition. There is a duty to produce findings that will benefit society and are unobtainable by other means, with the expected results justifying the study. "Unnecessary physical and mental suffering and injury" must be avoided and experiments must not take place if there is any prior reason to believe that participation may result in death or disability. The Code declares that the necessary degree of risk should never be greater than the humanitarian importance of the research question and there must be adequate provision to protect subjects from any risk of injury, disability or death.[29]

The Code demands that highly qualified people using the highest level of skill and care must carry out all experiments. Those in charge must be willing to terminate the study if there is "probable cause to believe, in the exercise of the good faith, superior skill, and careful judgement required of him (sic), that a continuation of the experiment is likely to result in injury, disability, or death of the experimental subject".[29]

The Declaration of Helsinki of 1964 and revised in 1975,1983,1989 and 1996,[30] modified the Nuremberg Code in a number of ways. This makes an important

distinction between therapeutic and non-therapeutic experimentation and includes rules to protect vulnerable subjects. The Declaration states that any risks must be in proportion to the benefit of an experiment and it also classifies a wider range of benefits, risks and harms than those stated within the Nuremburg code. It also asserts that all publications resulting from experiments must be accurate, and that reports that do not meet these guidelines must not be published.

Research is also governed by civil and criminal law and in addition, the majority of professional bodies,[31, 32] the NHS and other funding bodies such as the Medical Research Council[33] have guidelines governing research. However, these are mainly concerned with setting appropriate scientific rather than ethical standards. Such guidelines usually state that ethical committee approval is required, leaving detailed considerations to the individual committees themselves. The Declaration of Helsinki declares that the experimental protocol must be "transmitted for consideration, comment and guidance" for an ethical review by an independent committee.[30]

Every trial within the UK must obtain Multicentre or Local Research Ethics Committee (MREC or LREC) approval. RECs provide independent advice about the ethical status of clinical research within their geographic area and are independent of health authorities and NHS trusts. However, this does not guarantee that a trial will be 'ethical' or that there are uniform standards of acceptability. Kodish et al[34] point out that the various US Institutional Review Boards, set up to ensure the scientific and ethical standards within trials (similar to the role of ethics committees in the UK), have different standards of acceptability. A protocol may be accepted by one but be rejected by another. They believe that such variability in decision making may be the result of some boards focusing on protecting patients while others may be more concerned with the scientific standard of a trial, suggesting that patient autonomy is not always guaranteed by such approval.

The main ethical issue within the randomised controlled trial is that it must not exploit participants, who must also not be used purely for the benefit of others. The main focus of this debate is whether it is ethical for patients to receive experimental treatment that may be detrimental, ineffective or not as effective as the standard treatment. The trial may also benefit other future patients and any possible risks resulting from participation must be outweighed by the benefits to future patients. It is also argued by some that it would be unethical to give patients a treatment which has not been tested when a standard treatment is available.[35]

The exploitation of trial participants does not have to be intentional and may occur when patients are exposed to risks that could be avoided by using adequate technology or introducing appropriate safeguards.[36] The trial must be well designed (see chapter 2). Any randomised trial that does not use the best available methodology, from the design and planning through to the administration and statistical methods employed could be considered to be unethical.[18] If the poor quality of a trial's design leads to problematic results, then this is both unfair to participants and also a waste of resources.[37] The clinicians participating in research may be inefficient or incompetent and trialists must have the appropriate level of knowledge and training. De Castro suggests that trialists could be screened or regulated in some way to ensure competence.[36]

The research question must be valid and necessary. It would be unethical to run a trial where the question had already been answered. To ensure this does not occur, Herxheimer[38] suggests that all trial proposals must include a systematic review of previous studies examining the research question. Publication bias (the under-reporting of negative trials), can however, distort the available evidence. The Cochrane Controlled Trials Register within the Cochrane Library was set up in an attempt to ensure the availability of the results of all trials and to create a source of data on which to base systematic reviews which can be used to determine the validity of research questions. This register is a bibliography of controlled clinical trials that have been identified by contributors and includes

reports published in conference proceedings and other sources not covered by bibliographic databases.[39]

Design issues

The ethics of trial design focus on whether there is equipoise, the appropriateness of randomisation, blinding and placebos and the dilemma of which groups should be included or excluded from trial participation.

a) Equipoise

A trial must only be carried out when there is clinical equipoise, which exists when the evidence for treatments is balanced, and the clinician has no treatment preference. Fried first introduced the term "equipoise" (p.51)[40] and although this is often referred to as 'uncertainty' as to which is the best treatment, as Lilford and Jackson[41] point out, equipoise exists when there is no preference between the treatments being compared, a state where clinicians are "on the fulcrum of a decision" (p.552). Thus when there is clinical equipoise, personal care is not abandoned, rather chance is used to determine treatment assignment, each thought to be of equal benefit to patients.[42] Once evidence indicates the greater effectiveness of one of the treatments then equipoise no longer exists and a trial should not be mounted.[35]

However, as Freedman points out, such theoretical equipoise is "overwhelmingly fragile" (p.143) and can be disturbed by any slight change in the evidence which can be obtained from "the literature, uncontrolled experience, considerations of basic science and fundamental physiologic processes, and perhaps a 'gut feeling' or 'instinct'" (p.143).[43] Levine similarly argues that perfect equipoise rarely exists and that when it does, this state cannot be maintained for long.[44] As Fried notes, "is it ever likely to be the case that in a complex medical situation, the balance of harms and benefits discounted by their appropriate probabilities really does appear on the then available evidence to be in equipoise?" (p.52).[40] For a trial to be ethical, then, the research hypothesis must be simple enough to allow such a balance to exist.

The practical aspect of the dilemma of equipoise means that clinicians often have difficulty accruing patients. A number of studies indicate that the requirement of an open discussion of clinical equipoise with patients is an obstacle for many recruiting clinicians.[43, 45-48] The justification for many appeared to be that any discussion of uncertainty is not in the patient's best interests. For example, many recruiting oncologists believed that such disclosure undermined patient confidence,[48] reduced patient morale[47, 49] and could lead to an increase in patient morbidity.[48]

Many clinicians appear to prefer to trust their own experience, even if this is in conflict with the available evidence. For example, the majority (67%) of an international sample of breast cancer oncologists (n=484) regarded clinical experience as the most important part of decision making where there was such uncertainty, with only 33% preferring published evidence.[45] In an examination of US oncologists' patient logs, Hunter et al found that the recruiting clinician's preference for a treatment was the main reason for the non-participation of half the eligible patients, especially amongst those eligible for phase II trials.[50]

Even where those running a trial hold clinical equipoise, those recruiting patients onto a trial, often nurses or junior staff, may not be in equipoise.[49] For example, Alderson found high levels of ignorance about equipoise among breast cancer clinicians (n=40). Although there were high levels of concern about the uncertainty of breast cancer treatment and the associated high levels of mortality within the wider profession and the press, only 23% were similarly 'very concerned' about current knowledge.[49] Such issues can have consequences for trials[51] (see chapter 2).

In response to the problems of traditional individual or 'theoretical' equipoise, Freedman suggests the use of "clinical" or community equipoise, which only calls for uncertainty within the medical community as to the efficacy of the treatments.[43] The argument here is that community equipoise is a preferable requirement because the aim of all trials is to answer disputes within the wider

medical community where there is a lack of consensus as to which are the most effective treatments.[44, 52]

Using this approach, recruiting clinicians with a treatment preference must recognise that other respected colleagues hold different preferences. Freedman suggests that even where the recruiting clinician's personal equipoise is in conflict with the community equipoise, a trial is still valid and ethical because "progress in medicine relies on progressive consensus within the medical and research communities" (p.144). Community equipoise can also be maintained even when interim results from a study suggest that one treatment may be preferable, because it can be preserved until the evidence is strong enough to influence the whole community of clinicians as to the effectiveness of the treatments.[43]

However, Gifford[52] does "not believe that community equipoise can do what it was hoped it could" (p.148). Both Gifford and Lilford and Jackson suggest this is a problem of definition and that it is hard to establish the extent of such equipoise.[41, 52] For example, how is the community opinion reached, and should this be based on the opinion of a small group of experts or all clinicians? There is also the difficulty of the level of uncertainty that is required and what proportion must be uncertain.[52] Johnson et al[53] point out that opinion within the medical community will rarely be equally divided. To establish the extent of disagreement within the medical community necessary for community equipoise to exist and for a trial to remain ethical, they carried out a trade-off survey of a sample of the public, nurses and medical students (n=113). Half the participants believed equipoise would be disturbed in situations where 70% or more of the clinical community were in favour of one of the treatment options.[53]

In cases where collective and personal equipoise differ or where both are required, this may have an important and often negative effect on trial recruitment. However, if only one is required, then there is the question about how to decide which takes precedence.[54] Chard and Lilford suggest that rather than impose a 'point' where equipoise is achieved, 'zones of equivalence' or

"equiphase" (p.5) would be more appropriate. Such equiphase would allow equipoise to exist within a range of probability estimates that are less restrictive than traditional equipoise. They argue that this approach would allow a more robust system of informed consent within trials.[54]

Personal equipoise, when an individual clinician has no treatment preferences, is also believed to be an important element of patient-centred ethics within medicine. If recruiting clinicians, based on their previous experience or patient history, suspect that one treatment may be more likely to benefit a particular patient, the use of randomisation within trials represents a compromise in individual care.[42] Levine maintains that clinicians have a duty to recommend what they believe to be the most beneficial treatment for a patient.[44] Similarly, Lilford and Jackson suggest that following collective equipoise, and entering a patient onto a trial when the clinician does not have personal equipoise and does not state this preference, may be a violation of doctor-patient trust. They propose that personal equipoise is less important, however, where the preferred treatment is only available within the trial.[41]

Peto and Baigent believe that trial accrual should use the uncertainty principle in order to bring the process of informed consent closer to standard medical practice.[12] Using this approach, patients are only entered into a trial if the recruiting clinician is uncertain as to which treatment is best for each individual patient. If the clinician or patient believe that there are any medical or other reasons why one of the trial interventions may be unsuitable for that individual patient then they should not be recruited onto the trial.[12] Similarly, Kodish et al[34] argue that clinicians should only enrol patients onto a trial if they do not have a preferred treatment for that particular patient. While accepting the clinician's right to base their decision on their personal belief about the acceptability of treatment within a trial, Segelov suggests that such decisions should be documented to ensure that they are not based on "nonscientific, whimsical feelings" (p.104).[55]

Stopping rules

However, equipoise can be disturbed by such things as interim data and thus there is the additional ethical problem of what should be done if the result of a trial become apparent before the trial has been completed. Although clinical equipoise may have been achieved at the start of the trial, this may be altered by preliminary information from data monitoring, which may indicate that one of the interventions is more effective.

There is no agreement on the ethics of having a predetermined endpoint for trials. The main argument against its use is that to continue a trial until a certain point of significance is deceptive. In using this approach, trialists must pretend that they have no access to data because they have agreed not to examine it. Others argue that the use of a pre-agreed endpoint is ethical as long as patients are informed of this prior to enrollment.[56] It has also been suggested that interim data should be withheld from recruiting clinicians or that new trial designs be developed that can avoid any violation of the therapeutic obligation.[57]

b) Randomisation

Randomisation is considered in detail in chapter 2. Here, only the ethical issues relating to randomisation are discussed.

In their recent review, Ashcroft et al[35] point out that randomisation "divides the medical research community rather sharply" (p.7). The basis for this conflict is both methodological and ethical. Those in favour of random allocation suggest that this method does not abandon personal care, because randomisation is only ethical if there is clinical equipoise. Chance is used to determine assignment to a treatment, so that each participant is equally likely to benefit from the new or existing treatment. Other non-randomised research methods, particularly studies using historical controls, as Altman[18] shows, may be intrinsically unethical because their results are untrustworthy and support the use of ineffective treatments. As previously stated, any randomised trial that does not use the best available methodology is also unethical by exposing patients to unnecessary risk.

However, there is evidence to suggest that both recruiting clinicians and participants find randomisation problematic. Randomisation can be viewed as a compromise in individual care and as McPherson indicates, the issue of preferences (clinician or patient) is also important, with random allocation depriving patients of the benefit of treatment choice, preference and control which may have a therapeutic benefit.[22] Even though from the clinician's perspective, a trial may have achieved equipoise, a patient's personal circumstances may mean that they have a preference for one of the treatments.[34]

c) Representativeness

Representativeness is a key ethical issue for trials. If those who take part in the trial are not representative of the future population of patients whose treatment may be affected by the trial's outcome, it is difficult to interpret the subsequent findings and assess the generalisability of their results.

The under-representation of racial and ethnic groups participating in clinical trials needs to be addressed by trialists.[58, 59] Without their participation, the results of trials may not be applicable to these populations.[58] This may be particularly important for example, in trials of malignancies such as myeloma, cervical and oesophageal cancers, where there are substantial epidemiological and clinical differences between Black and White populations.[59] Ashcroft et al similarly conclude that trials must not focus their eligibility criteria on certain sub-groups within the population unless there is clear justification for doing so.[35] In a contrasting view, Peto and Baigent emphasise that that some findings are generalisable to wide population groups and that it is not possible or ethical to carry out trials on every population and every sub-group, because with small samples the resulting selection bias will produce greater errors, and inevitably it would mean withholding effective treatment from some participants.[12]

The ethics of excluding eligible patients

The ethics of not entering eligible patients into a trial must also be examined. Segelov et al[55] argue that it is unethical not to enter eligible patients onto a trial

because this contradicts clinical equipoise and assumes that the recruiting clinician knows which is the most effective treatment. They suggest that once the ethics committee within an institution has agreed to the trial, they are acknowledging that there is equipoise and that trial entry should be the standard treatment in such circumstances.[55]

d) The use of placebos

A placebo is an inert substance used to ensure that neither the individual clinician nor the patient knows the allocation within a double-blind drug trial. The ethical principle of equipoise means that unless the placebo is believed to be as good as the existing treatment, it is unethical to assign patients to a placebo.[60-62] However, advice on the use of placebos is inconsistent.[61] It has been found that many recent trials have used placebos in circumstances where an effective therapy is available but has been denied to participants. They highlight that trials of rheumatoid arthritis, Ivermectin (to treat river blindness), Ondansetron (to control chemotherapy-induced emesis) antidepressant, congestive heart failure and antihypertensive drugs have been particular areas where this has occurred.[62] The Declaration of Helsinki states that "in any medical study, every patient-including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method".[30] On this basis, the use of placebos and 'active' experimental treatments could be considered unethical.[61] The Helsinki Declaration has been criticised for this position, with many arguing that such statements must be revised.[60, 61]

Trials of new drugs are held to be scientifically strongest when there is a placebo control.[13, 15-18, 62] One of the main arguments for the use of placebo is that it provides a clear benchmark as to whether a new treatment is better than nothing. However, there are considerable 'placebo' effects (improvements are commonly found with the use of an identical but inactive intervention) and as Bradford Hill points out, the aim of trials is to establish the effectiveness of treatments against the standard treatment, not whether it is better than nothing.[63]

Determining the effectiveness of treatments is not always clear. For example, although a treatment may be therapeutically inferior to the standard treatment, it may be beneficial in other ways, for example by providing better quality of life. Hence it can be argued that for some patients, the adverse effects of a treatment may balance the therapeutic benefits sufficiently to ethically justify the use of placebo. However it is not ethical to use a placebo as a means of avoiding making the often complex decision as to which is the standard treatment.[62] Placebos are often preferred for scientific reasons because it is easier to demonstrate a statistically significant difference between an active treatment and placebo, even within small trials. However even in situations where the use of active controls are difficult, "scientific considerations should not take precedence over ethical ones" (p.396).[62]

The use of placebos is often justified because in some cases withholding a standard treatment will not cause serious harm, for example in the treatment of nausea, which will result in no long-term effects for patients. However, although this may seem acceptable, this is in conflict with the fundamental ethical principle that patients should receive the best available treatment or a new treatment believed to be of equal or better effectiveness.[62] It is also argued that placebo trials are ethical where patients are fully informed that they may not receive an active treatment and are aware as to the risks of participation. However, this passes the ethical burden onto the individual patient who, even if they accept, must not be placed in the position where their well-being could be compromised.[35, 62] This is linked to the problems of providing informed consent[62] which are considered in more detail in the section that follows.

Informed consent

The first principle of the Nuremberg Code states that "the voluntary consent of the human subject is absolutely essential".[29] A fundamental ethical requirement of the randomised controlled trial is that patients must give their informed consent to participate. Changes in medical knowledge and the development of research in medicine have led to an increasing respect for patient autonomy as a

central moral imperative, even though this was unheard of until relatively recently.[64] The clinicians who provide informed consent are expected to ensure that patients receive all relevant information to make that decision.[36]

Exploitation of trial participants can occur when some form of deception has taken place during their recruitment. Patients must not agree to take part in a trial because they have false hopes or expectations of an intervention achieving a favourable outcome which is "less than reasonably likely" (p.261)[36] to happen. Such false expectations may be the result of receiving inaccurate information about a treatment's possible benefits and associated risks. This may not be deliberate, as recruiting clinicians may believe that some information is not necessary and this can occur particularly if there are cultural or socio-economic differences between the recruiting clinicians and participants.[36]

Although the use of guidelines and regulations governing research can minimise the potential for exploitation, they must be able to take into account differences within society, such as the position of vulnerable groups. There is potential for exploitation through an imbalance of power between the researcher and the researched, which may lead patients to participate in research which in other circumstances they may not have agreed to.[36]

Some take the position that such a violation of the doctor-patient relationship can be justified, for example by the use of informed consent and the minimisation of potential harm.[57] A stronger position states that the RCT must be abandoned because it is inconsistent with the doctor-patient relationship and the doctor's therapeutic obligation to treat a patient in a manner that will ensure the best chance of recovery. This latter perspective suggests that new scientific methodologies must be developed which are consistent with the doctor-patient relationship. Concurrent matched-pair analysis has been suggested as one method of achieving this, where clinicians in favour of one of the treatment options, prescribe to their patients accordingly.[65] However, this approach can introduce bias and we do know that RCTs generally provide the most reliable and unbiased evidence.[57]

A Lancet editorial suggests that potential trial participants should be informed specifically about the components of research that constitutes a change from the standard doctor-patient relationship. These central differences are randomisation and blinding, plus any additional clinical examinations and therapies.[66] Edwards et al similarly conclude in their review that abstract concepts such as randomisation should receive particular attention, "since it is the conceptual scientific basis of trials rather than details of the treatments themselves which patients find hard to grasp" (p.53). It is also important that participants understand equipoise and thus have realistic expectations of the benefits of trial participation.[67]

The main tool used to avoid exploitation of subjects is the consent form, which is a legal document. This and the procedure of providing informed consent should ensure that participants receive all the relevant information about the trial and that the perspectives of all interest groups within the trial are adequately represented.[36] Interestingly, the consent form is generally perceived by trial participants, to be a legal document protecting those running the trial rather than educational.[68-70] Harth and Thong found that 14.5% of parents (64) thought informed consent was unnecessary because they trusted the clinician to give their child the best treatment.[69]

The UK General Medical Council has recently issued new guidelines to doctors obtaining consent. This recognises that the information provided to patients will be variable and should be based on the individual's needs and priorities.[71] Information should not be withheld unless it is believed that such information would cause serious harm to the patient. It goes on to state that doctors should not make assumptions about patients' views and also cautions that patient compliance with procedures should not be interpreted as consent.[71]

However, the quality of the informed consent procedure and subsequent reporting is highly variable.[72] Research examining informed consent has found that even when trials adhere to strict informed consent procedures and ensure that 'simple language' is used, this does not guarantee that subjects will fully

understand the implications of participation and that they may still have unrealistic treatment expectations. Harth and Thong, for example, found that trust in the medical system, the tendency of patients to lessen the potential risks of participation and the psychological need to volunteer were 'significant attitudinal barriers' to the informed consent process and hence the understanding of trial participation.[69] When participants do not understand what they have consented to participate in, then this does not constitute truly informed consent.

Edwards et al suggest that ensuring that all patients achieve fully informed consent is "an unobtainable ideal" (p.vi).[67] Their recent review suggested three approaches to dealing with this issue. One option would be to conclude that all trials are unethical unless the participants are medical experts or alternatively, waive all requirements for obtaining informed consent and instead use other safeguards such as ethics committees to protect participants. The approach preferred by Edwards et al would be to retain the essence of the informed consent principle by ensuring that all practical measures are taken to increase participants' understanding with the additional protection of ethics committee safeguards.[67]

Recruiting clinicians commonly find obtaining informed consent a barrier to recruitment.[45, 47, 48, 73, 74] For many this is based on a dissatisfaction with the rigid format of the consent form[48, 73] or because it highlights their dual role as physician and investigator.[48] Such barriers can affect the development and uptake of trials. For example, the introduction of explicit regulations for a clearly defined process of informed consent describing both the risks and benefits to potential participants, led to a subsequent drop in the number of breast cancer trials being carried out.[49] Alderson concluded that providing such explicit information to patients may be problematic for clinicians.[49] Clinicians have also been found to screen patients by trying to predict who would have difficulty with the informed consent process and thus enrol only some of their patients onto trials.[47, 75, 76] Kee believes that paternalism is still prevalent within medicine,

with clinicians still believing that they can make the best therapeutic decisions for their patients. It is highly questionable as to whether clinicians are better able to interpret medical evidence than patients themselves.[77] Given the importance of the clinician in recruiting patients onto trials, it is surprising that little research has investigated their role.[78]

Edwards et al[72] in a recent (1998) systematic review of the ethics of the RCT from the perspective of patients, the public, and healthcare professionals concluded that a surprising number of recruiting clinicians were aware that their patients did not fully understand what trial participation involved, "For many, informed consent seemed little more than a ritual" (p1212). This will be explored in more detail in chapter 3. Edwards et al conclude that there may be significant differences between trialists and ethicists as to what is ethically acceptable and suggest that there should be a greater public debate about ethics and medical research. Zwitter and Tobias similarly acknowledge that there may be a wide gap between the investigator's beliefs about informed consent and patients' actual understanding of the trial.[79]

Information provision

The ethics of providing greater information has also been debated. It has been argued that greater provision of information to patients is "needlessly cruel" (p.1199)[80] by promoting greater anxiety among patients and thus a negative effect on the doctor-patient relationship. Taylor and Kelner similarly found that the majority of North American and European oncologists (n=170) believed that the admission of uncertainty undermined patient confidence (91%) and could increase patient morbidity (73%).[48] However, it has been suggested that the open discussion of clinical uncertainty may actually encourage trust and improve the doctor-patient relationship.[81] Recruiting clinicians may need more support and training to deal with providing informed consent and acknowledging such uncertainty.[82]

From the perspective of participants, Jensen et al found that the majority of women within a breast cancer trial (26) believed that the detailed information

they received had reduced their uncertainty and anxiety.[83] Although they found decision making difficult, this gave them responsibility for their own treatment and most felt that this helped them to face their prognosis. Only two believed that this information had increased their anxiety, preferring their treatment to be chosen by the doctor or to be randomised without their knowledge. Jensen et al concluded that because these doctors were open about their uncertainty, this preserved patient trust.[83]

In contrast, Olver et al found that patients experienced differing levels of anxiety from the information they received. Although 21% of participants in an oncology trial felt that detailed information reduced their anxiety, a similar number (19%) believed it increased their anxiety.[70] White et al also found that even though the majority of breast cancer patients (65%) preferred to receive detailed information, 20% preferred a consent form which merely stated that they had been selected by the clinician to receive a specific treatment which was beneficial for most patients.[84]

Kent suggests caution is necessary because it is not known whether information will actually decrease or increase anxiety among patients.[85] In a recent review of the literature on patient participation in decision-making, Guadagnoli and Ward conclude that patients do want to be involved in decision-making and be informed of the alternative treatments. They suggest that the first step in this process must be to establish the level of decision making patients believe is appropriate.[86]

Voluntary consent

An important principle of the RCT is that participation must be voluntary. However, there is some debate surrounding the true voluntary nature of trial participation. For example, Kodish et al point out that willingness to participate in trials may be affected by patients' preferences for a treatment, especially when that preference is only available within the trial. They suggest that the frequency of unwillingness to be randomised could be used as an indicator of such inequality between the treatment options from the patient's perspective.[34]

Minogue et al[87] argue that patients with a terminal condition should not be recruited onto trials because the seriousness of their condition precludes genuine volunteering. They suggest that trials should only randomise patients who are motivated by a wish to contribute to medical knowledge or those who are not 'desperate'.[87] They believe 'desperate volunteers' who want to receive the experimental treatment should be given the option of either participating in the trial or receiving the experimental treatment outside of the trial. However, in response to Minogue, Logue and Wear[88] argue that such an approach hinders medical progress and fails to provide an appropriate clinical response to such patients. Thornton in a personal account, believes that asking patients to participate in a trial when they have just received a cancer diagnosis is ethically unacceptable, damaging the doctor-patient relationship and leaving patients feeling isolated at a time when support is vital.[89]

Providing financial compensation may also hinder voluntary participation because this may impede a patient's ability to realistically weigh up the benefits and disadvantages of participation.[90] This is the case even though not compensating patients for any risk or inconvenience caused by participation may also appear to be exploitative.[36]

Informed consent in clinical trials

A far more stringent standard of providing informed consent is required for clinical trials, which are considered to possess a higher risk than standard treatment, even when the same treatment is prescribed outside of a trial. The issue of experimentation is the main reason for this, because of the way research changes the doctor-patient relationship and because research is also for the benefit of future patients.[64]

However, as an editorial in The Lancet points out, "clinical decisions are often made randomly in a haphazard way. Why are we so concerned when the randomness is formalised in a controlled trial?" (p.806).[66] Chalmers[91] refers to this as a "malignant double standard" (p.337) and argues that the informed

consent requirements should be equivalent for all patients, whether they receive standard treatment or participate in a trial.[91]

Trialists believe that the evaluation of therapies is not in conflict with patients receiving the best care because participation in such trials is the most effective way for patients to receive the best available treatments.[64] Trials that meet clear criteria, are well designed, set out to answer a clinically important question and where there is a belief that the treatments are equal on the evidence so far, offer patients treatment which is at least comparable to treatment outside the trial and thus constitutes good medical practice.[92] Trial participation will result in some loss of freedom in their allocation to a treatment and this must be weighed against the benefit to future patients and the benefits of trial participation, regardless of the treatment allocation they receive.

It is often assumed that trial participants who are found to have received the less effective treatment at the end of the trial have been deprived of better treatment. However, as Lilford and Jackson[41] point out, this group may not have received better treatment outside of the trial and may be privileged patients who benefited from the extensive monitoring of the condition within the trial. Trial participants will receive one of the best therapies available and are likely to receive their treatment within a major institution with highly qualified staff where they are likely to increase the chances of a positive outcome.[44]

Although the regulations for experiments were originally from the perspective of protecting subjects from harm, since the mid 1980's and the rise of AIDS activism, trials have been increasingly perceived as offering patients a chance to gain access to the best available treatments.[44] There is evidence to suggest that patients receive better treatment within a trial. Stiller in a review of cancer survival rates found that treatment within a clinical trial was associated with improved outcome.[93] Davis et al similarly found that participants in lung cancer trials had an improved outcome over matched controls. They suggest that this may be due to differences in the evaluation, staging and follow-up of

participants, the quality of the surgery, a placebo effect or differences in patient motivation.[94]

The use of improved treatment protocols within trials can lead to improved outcome. Reiser and Warner[95] found improvement in the condition of participants within three paediatric asthma trials who did not receive active treatment. Although they recognise that this may be a placebo effect, they suggest that this may be due to the improved management of their condition. Trial participants had regular, lengthy consultations with a specialist, received training on how to control their symptoms which increased participants' motivation and compliance.[95] Karjalainen and Palva similarly found that patients within the same geographic area as three trials of chemotherapy in Finland had an improved survival compared to patients living in other areas.[96]

However, any such benefit of participation should not be part of the decision to take part and should not be used by recruiting clinicians as an inducement to participate.[67] This would violate the Helsinki principle that non-participation will not affect the patient's standard of care.[30]

Inequalities in informed consent

It is often stated that obtaining informed consent to participate in a trial from poorly educated patients is a 'sham'.[66] However, the data examining inequalities in the comprehension of informed consent is contradictory. Some studies have found socio-economic differences in comprehension. For example, Harth and Thong found that parents who volunteered their children were "significantly more socially disadvantaged and emotionally vulnerable" (p.1375) than those who did not.[97] Higher levels of understanding amongst participants with a college education have been found[98] and similarly, Howard et al found that education, ethnicity and age were all associated with participants' awareness of fundamental aspects of the Beta-Blocker Heart Attack Trial (BHAT).[98] In contrast, Flanery et al found that a well educated population of mathematics and medical undergraduates also had problems understanding consent forms.[99]

The DCCT Research Group evaluating the informed consent procedure within a US diabetes treatments trial found no relationship between IQ and comprehension.[100] Sussman et al,[101] Goodman[102] and Gallet et al[103] similarly found no evidence to suggest that age influenced understanding.

International differences in providing information

There are international differences in the requirement of informed consent and the guidelines within trial protocols for obtaining informed consent vary widely between countries. Zwitter and Tobias found for example, that over half the principal investigators of 47 international lung cancer trials (1993-1995) reported that patients were often not told about their diagnosis and prognosis (40%) and that written informed consent was only required within half of these trials (55.8%). Patient information about diagnosis and prognosis (96.2%) and the requirement of written and signed informed consent (100%) was highest within the North American studies. Within other countries surveyed, patient information about diagnosis and prognosis (49%) and the requirement of written and signed informed consent (41.8%) was less than half that level and often provided only verbally (54%). However, this study relies on the reporting of the principal investigator and the authors speculate that there may be a wide gap between the investigators' beliefs about their informed consent procedure and its implementation.[79]

Prior to 1980, clinical researchers in Canada were not required by ethical guidelines to inform trial participants that they had been randomly allocated to the treatment they received. Similarly, obtaining informed consent from patients before entering them onto a clinical trial was not mandatory in Spain until the early 1990's.[104] In Sweden, although it was recommended that the informed consent procedure should involve both oral and written provision of information, in 1991 it was still being debated whether written consent should be a requirement.[105]

Conclusion

The debate on the ethics involved in RCTs has focussed on whether there is equipoise, the appropriateness of randomisation, blinding and placebos and the dilemma of which groups should be included or excluded from trial participation. These debates have influenced the design of the RCT and this will be discussed further in the following chapter.

Much of the attention has been placed on the importance of the informed consent procedure. However, the quality of the informed consent procedure and subsequent reporting is still highly variable[72] and there appears to be a wide gap between investigators' beliefs about informed consent and patients' actual understanding of the trial.[79] There is little from the patient's perspective. Ashcroft et al in their review conclude that there must be "a shift in research emphasis away from ethics from the professional viewpoint and toward the lay point of view" (p.45).[35] This will be discussed in more detail in chapter 3, after a consideration of the methods of RCTs.

Methods of the randomised controlled trial

This chapter considers the methods of the randomised controlled trial. In the section that follows, general aspects of RCTs are described, followed by an examination of issues specific to the design, organisation and planning of an RCT. Randomisation, concealed allocation, blinding, placebos, bias, validity, outcome measures, compliance, and preferences are each covered.

Introduction

There is an increasing reliance on the RCT, often regarded as the 'gold standard' within clinical research. The basic rationalisation behind the clinical trial is that it is comparative rather than representative.[106] The RCT sets out to measure and compare outcomes, that is, the events that are present or absent after participants have received the trial intervention.[13] This outcome measure may be "death, a nonfatal clinical event or a laboratory test" (p.3)[16] and can take the form of survival, disappearance of symptoms, reduction of symptom severity, speed of recovery and/or the prevention of symptom recurrence.[15] The results of such trials are then used to make inferences about the effectiveness of the interventions within a relevant patient population.

A trial usually involves one or more experimental interventions and a control. The experimental treatment can, for example, be a new drug or procedure, whilst the control is the intervention that is regarded as the standard for comparison, usually routine practice, or where none exists a placebo or no intervention. The quantity and type of such interventions and the subsequent treatment regimen are decided upon by the trial investigators.[13]

The RCT is ideally suited to examine, as Jadad points out, "the effects of health care interventions which are small to moderate" (p.8).[13] However, the RCT is not appropriate to explore questions associated with the aetiology or natural history of diseases. Here cohort or case controll studies are more appropriate.

In the section that follows, general aspects of RCTs are described, followed by an examination of design issues specific to RCTs.

Traditional trial methods

Decisions about the design of a trial are dependent upon a number of factors: the type of intervention trialists wish to examine, the method of providing patients with the intervention, whether patient preferences are being taken into account and sample size required.[13] Explanatory and pragmatic trials and phase I, II and III trials all evaluate different aspects of an intervention. Parallel, crossover and factoral trials are related to the method of exposure of participants to the trial intervention. Trials also differ in size, from n=1 up to mega-trials which can be fixed or flexible (sequential trials).[13]

Explanatory and pragmatic trials

RCTs are often distinguished by whether they evaluate the efficacy or effectiveness of an intervention. Efficacy trials are designed to produce a basic evaluation of an intervention and are therefore explanatory trials. Effectiveness trials are designed to establish whether an intervention is effective within the population who have received it and are pragmatic.[13] Thus the two main approaches to the design of a clinical trial are the pragmatic and explanatory[107] and in general it can be said that "the first approach (pragmatic) regards the patients as an end, the second (explanatory) as a means" (pp.58-59).[17]

An explanatory trial examines the efficacy of an intervention, for example, whether a drug or treatment is effective under certain conditions.[13] This type of trial usually employs strict inclusion criteria to ensure patients reflect a specific definition of the disease under investigation. Analysis is confined to compliers only- that is, patients who received the treatment according to the protocol,[15] with the focus on clinical outcomes such as death, flow rates and blood tests.[13] However, protagonists of pragmatic trials believe that limiting the analysis to patients who adhered to the treatment protocol can distort the comparison of

treatments by its inability to demonstrate the effectiveness of an intervention in real clinical practice.[15]

The pragmatic approach is increasingly preferred because "it provides a more valid assessment of treatment efficacy as it relates to actual clinical practice" (p.182).[15] The aim of a trial using this approach is to determine the effectiveness of the intervention in circumstances that attempt to imitate clinical practice.[13] To achieve this, pragmatic trials have wider inclusion criteria than explanatory trials with the aim of reflecting the patient population, usually use active treatments as controls, and provide flexible treatment regimens. Pragmatic trials often use a wider range of outcome measures that attempt to assess quality of life and take into account factors such as side-effects, cost and complexity.[13] Randomisation determines how patient data are analysed as well as their treatment allocation, hence within this type of trial, patient randomisation should be carried out as late as possible.[108] Data analysis is by intention to treat and all patients randomly allocated to an intervention are analysed as one randomised group, regardless of whether they completed or actually received that intervention.[17, 108] The advantage of this approach is that it aims to reflect the effectiveness of interventions under the conditions of normal clinical practice. Hence, Brewin and Bradley suggest that pragmatic trials are most suitable for testing interventions that require patient participation: an explanatory design may underestimate the effectiveness of such interventions because they are unable to take such factors into account.[109]

The main objection to the pragmatic approach is that it includes in the analysis of an intervention, participants who did not actually receive this treatment. Using this approach, however, does allow for data to be analysed as for an explanatory trial. Proponents of this method argue that all patient outcomes after randomisation must be included in the analysis of an intervention because this reflects the normal pattern of practice where there are often inherent delays or patients who cannot receive a treatment for various reasons. This approach also

allows the sequence of treatments to be considered in the evaluation, including adverse outcomes or switching to an alternative treatment.[108]

Different interventions

Within RCTs, the method of participants' exposure to the trial intervention may differ. The principal methods are parallel, crossover and factorial trials. The parallel design is used in the majority of RCTs and provides between-group comparisons. Here, each patient group receives only one of the treatments available within the trial.[13]

Within crossover trials, patients receive a sequence of interventions at different points within the study and these treatments are evaluated using within and between-patient comparison. Using this approach, patients act as their own control. Smaller samples can be used and bias can be avoided through the random allocation of the initial treatment.[15] The two-period crossover trial involves two treatment sequences. Respondents are randomised into two groups: the first group are given treatment A and after a wash-out period are given treatment B, while the second group are given treatment B, then a wash-out period followed by treatment A. More complex designs can also be carried out; for example, multi-period crossover designs include more than two treatments and examine the short-term response to treatments, with patients acting as their own control.

In theory, crossover trials allow the precise comparison of treatments, but this method is only appropriate for examining stable, chronic or incurable diseases with relatively rapid outcomes. Problems associated with this design include low statistical power, time effects and possible carry-over effects of each treatment.

Factorial trials are employed when it is necessary to evaluate an intervention both separately and combined in order to assess the interaction between therapies and compared to a control treatment.[13]

Different types of sample sizes

Sample sizes within RCTs can be fixed or flexible and can vary from n=1 up to mega-trials with thousands of participants. *N*-of-1 trials are used to provide information on whether a treatment will help a particular patient (usually with a rare condition), rather than provide generalisable results. They are similar in design to the crossover trial, with one patient given the trial interventions either combined, randomised or on a number of occasions.[13] At the other end of the scale, "mega-trials" (p.19) are increasingly being advocated[12] and used. These are simple, pragmatic trials which examine large samples of patients and employ a limited number of outcome measures.[12, 13] However, Charlton argues that mega trials are not hypothesis testing but are in fact inductive, using a level of analysis at population level to assess representativeness and as such should be regarded as a form of epidemiology.[51]

Sequential trials are based on the parallel trial design, although in this case the sample size is not fixed, and participants are recruited until a difference between the interventions is established. Jadad believes that although this type of trial can be more efficient than fixed sample trials, for this design to be effective, the main outcome measure must be obtained as soon as possible after participants have entered the trial.[13]

To obtain a realistic calculation of the size of trial it is important to estimate the accrual rate necessary and assess the subsequent resources needed. Pocock emphasises that this calculation must be realistic, and take into account that the number actually recruited to a study is often less than half the original estimate.[15] Some clinical trials are terminated because such estimates fail to take into account the proportion of patients who will be ineligible or may refuse to participate.[110] As a general rule Pocock states that the accrual period should be no more than two to three years.[15]

To ensure that a trial has a strong chance of detecting a statistically significant difference between the interventions, if such a difference exists, sample size calculations are used. To obtain this, the minimal degree of benefit that a new

treatment would have to achieve in order for it to be preferable to the standard treatment is estimated. Sample size calculations should be based on the primary outcome measure(s) and the power of the hypothesis test. A power calculation of 80-90% is commonly used and the greater power achieved, the greater the possibility of detecting such differences, although to obtain this, larger sample sizes are required.[18]

Types of trials

Clinical trials are funded by pharmaceutical companies, research councils such as the MRC, the NHS through the Health Technology Assessment (HTA) programme and regional R&D directorates and other nationally based health organisations.

There are four phases of experimentation, which in general are part of the research programme for the development of a new drug, treatment or technology. Phase I trials take place once the safety and possible efficacy of a drug have been tested on animals. Trials at this stage are usually a series of cases and are mainly concerned with safety and the identification of the optimum dosage of the drug without causing serious side effects. Participants within this type of trial often have conditions for which there is no other effective treatment, such as HIV and some cancers. The next stage, Phase II trials, involves small-scale studies (usually approximately 20 patients) examining the efficacy and safety of different doses of a drug. This stage is effectively a screening process to identify whether a drug has potential benefits.[13] Phase I and II trials are usually explanatory.

The full-scale evaluation of a treatment is obtained from Phase III trials. For example, once a drug has successfully completed phase II, it is then compared to the standard treatment(s) or placebo and at this stage, patients are usually assigned randomly to the different treatments.[15] These are generally pragmatic (effectiveness) trials.[13] Phase IV trials use longitudinal methods to examine morbidity and mortality to identify any adverse effects of the drug. In drug trials, this stage is often linked to the post-marketing surveillance of a drug.

Specific design issues of trials

A number of specific issues are involved in the design, organisation and planning of a randomised controlled trial. Randomisation, concealed allocation, blinding, placebos, bias, validity, outcome measures, compliance, and preferences are each covered below.

Randomisation

Randomisation is one of the central precepts of experimental methodology and is generally accepted as the most efficient and preferred method of patient allocation within the RCT. As Pocock, states, "such plans to eliminate bias are the key to a successful trial" (p.9).[15] The alternatives to randomisation, such as systematic assignment and judgement assignment are likely to lead to biased and overoptimistic results for new treatments (see further below).

Randomisation, as Altman points out, does not mean that allocation is "haphazard" (p.86), but that patients have an equal (or known) chance of being allocated to any of the trial interventions.[18] Random allocation is used to address within-trial variation, by distributing any known and unknown factors between the treatment groups[106] and thereby reducing the risk of serious imbalance of factors between groups which could affect outcome.[13] By ensuring that the intervention groups are similar, it is hoped that the trialists will be more likely to identify and measure the effect of the intervention, with minimal influence of other factors which could affect the results.[13]

However, even if randomisation is used, bias may still be present[13] and it does not necessarily balance the distribution of known or important factors that may influence the outcome of the trial.[106] Randomisation does allow, however, the clear comparison of groups at baseline and differences can then usually be accommodated within the statistical analysis.

Surprisingly, few studies have examined recruiting clinicians' attitudes to randomisation. The few studies that do, indicate that recruiting clinicians may find randomisation problematic. For example, Alderson found that although 39%

of breast cancer specialists approved of randomisation in principle, they preferred the limited certainty of personal care. Randomisation was the main reason this group did not recruit their patients onto trials.[49] McLean found that many Canadian trialists were uncomfortable with the disclosure of information about the random allocation to patients, believing it would lead to a fall in patients' willingness to participate.[111] In contrast, the majority (73%) of oncologists and haematologists within one US state (Maine) believed that randomisation was not an obstacle to recruitment, although this may reflect the lack of anonymity of this sample.[78]

Because of such attitudes there are concerns that recruiting clinicians may in some instances, attempt to distort randomisation. Schulz relates that during the course of 20 epidemiology workshops with clinicians over 8 years, over half of the participants admitted that they had deciphered or witnessed someone else deciphering the assignment sequence. Although anecdotal, this does indicate that this problem cannot be treated as just a rare occurrence. He suggests that such behaviour may occur because fundamentally, "RCTs are anathema to the human spirit" (p.1457). Even if recruiting clinicians understand the need for trials, once they are participating they may experience conflicting interests. "Trial procedures attempt to impede human inclinations" (p.1457), and although deciphering may be a deliberate attempt to alter the trial findings, more generally it may be "an innocent reflection of human inquisitiveness and ingenuity rather than scientific malevolence" (p1457).[112] Yet such failure to adequately conceal randomisation can lead to the distortion of the treatment effects.[113]

Concealed allocation

Most clinical trials use a list of consecutive random treatment assignments that have been prepared in advance to allocate participants. Clinicians must not know the order of these lists and patients should be formally identified and registered before the treatment assignment is revealed. Common methods of concealment are sealed envelopes or drug packages with identical intervention or placebo

prepared by a pharmacist in the case of double-blind trials. For multi-centred trials with a central registration office, treatments can be assigned over the telephone. For all trials 'independent' trial personnel should be responsible for patient registration and randomisation.[15]

There are various methods of randomisation. Stratified randomisation is used to ensure that treatment groups are comparable and contain equal numbers of patients with certain characteristics that may affect outcome such as age or functional status. Crucially, any variable used for such stratification must be "prognostically important" (p.89).[18] As Altman points out, although many studies stratify by age and gender, only age is a known prognostic and gender should not be used to determine allocation in this way.[18] Stratification based on patient characteristics is a useful tool for small scale trials that are well organised and where factors known to affect response have been identified.[15]

When necessary, minimisation can be used to ensure that several variables are distributed as evenly as possible between groups.[18] Using minimisation, the next patient is assessed using the stratification variables to establish which treatment allocation would reduce the overall disparity between the groups at that point in patient accrual. Randomisation is then weighted in favour of this allocation. This method ensures that there is a balance of various prognostic factors, even within small samples and is mainly suitable for small trials or where small groups of patients are accrued from a limited number of recruitment centres.[18]

Although usually it is individuals who are randomised, cluster randomisation can allow allocation in groups. This is often used when it is not possible to randomise individuals, for example, within institutions (such as hospitals or GP practices), families or locations.[18] Individuals can also be a cluster, with repeated measurements taken from the individual. Cluster randomisation may be appropriate when an intervention may affect more than one person within the group or when the effect of an intervention on an individual may affect other participants (contamination).[13] This method is thought likely to become

increasingly utilised as the need to evaluate the delivery of health services grows.[114]

Restricted randomisation is commonly used to ensure that there are roughly equal numbers within the intervention groups by creating 'blocks' of random sequences.[13] It is standard practice to have roughly equal numbers of patients' randomised into each treatment group. However, weighted or unequal randomisation, which allows unequal numbers within groups while maintaining a distribution of characteristics across groups can be used for a number of reasons[13]. Trialists may wish to allocate fewer participants to the experimental treatment for a number of reasons. For example, if there are concerns about possible adverse reactions to an intervention; to monitor the learning curve of a new treatment; when the expected drop-out or crossover rate is likely to be greater for one of the interventions; when unequal variances are expected between interventions or for rare conditions. This may also be appropriate where it is possible to include historical controls within the standard treatment group, so that a greater proportion of patients can be allocated to the experimental intervention. This approach may also have economic benefits by providing the maximum statistical power for the minimum resources.[115] Unequal randomisation is useful, but if the differences in sample size between groups are great, then this can diminish the statistical power of the trial.[15]

Concealed random allocation is important to avoid bias[116] (see further below). Kunz and Oxman, in their review, found that failure to conceal adequately can lead to the distortion of the treatment effects in either direction, leading to either larger or smaller effects than is actually the case.[113] For example, Schulz et al found that inadequately concealed randomisation led to estimates of effect which were 30-40% larger than trials which were believed to have adequately concealed allocation.[117] Schulz points out that although sequentially numbered, opaque, sealed envelopes or pharmacy allocation, centralised or telephone randomisation methods are generally seen to represent the minimal standards required for concealed randomisation, they are met by only a quarter of current trials. There

is anecdotal evidence that some of these methods, for example, the use of envelopes, may still be open to subversion.[112] The description of randomisation and the methods employed are often poorly reported in published trials, even within principal journals, making it difficult to establish whether these studies have employed a truly random method of allocation.[13, 118] Kunz and Oxman conclude that the adequacy of concealment may be a more sensitive measure of bias within a trial than current quality assessment scales.[113]

Blinding

Blinding (or masking) is a methodological device to ensure that participants and sometimes clinicians are unaware which intervention has been allocated. The aim is to reduce "ascertainment or observation" (p.20) bias[13] (see below, pp.) which may occur if anyone involved in the trial knows which treatments patients are receiving. For example, if a patient knows their treatment allocation this may have a psychological effect: "one should not underestimate the importance of psychology in other non-psychiatric diseases: whether it be asthma, cancer or heart disease the manner in which patients are informed of therapy can have a sizeable effect on subsequent performance" (p.91).[15] Similarly, the clinicians involved in the treatment and management of a patient may be influenced by their knowledge of the patient's treatment. In an attempt to ensure unbiased evaluation, the evaluator should also remain unaware of which treatment patients are receiving (blinded evaluation). As Pocock states, "One key issue is to ensure that those responsible for assessing patient outcome are as objective as possible" (p.91).[15]

A double-blind trial refers to an RCT where both the patients and those responsible for outcome assessment do not know the treatment assignment.[13] Within a double-blind, double dummy trial, participants receive one of the active interventions or a placebo that is identical to the other active intervention. This is often employed when the interventions being compared are administered using different methods, for example, a trial comparing tablets with injections.[13]

Trials that are not blinded are referred to as open RCTs and are used where it is not possible to blind participants to the intervention, for example, comparing surgery with a drug. A single-blind trial is where one group, usually the participants or the investigators assessing outcome, have no knowledge of the intervention allocation. Senn suggests that such partially blinded designs should be referred to as 'veiled' trials.[106]

It is often argued that the inability of trials of surgery to be blinded is a major methodological problem. Single blind surgical trials have been carried out where a surgical intervention has been compared to a 'sham' procedure, however, there are ethical problems with such an approach. Russell argues that such problems can be overcome by the implementation of pragmatic trial designs and ensuring that the assessment of outcome is blinded. Those trials specifically comparing new procedures with standard ones should also take into account the experience of the surgeons performing the new technique and also randomise patients as soon as possible in order to evaluate the learning curve and short term costs involved.[119]

Placebos

To achieve blinding, the treatments being compared must be presented in an identical format. In a double blind drug trial, a placebo, an inactive substance which looks and tastes the same as the active treatment can be used.[13] However there are a number of problems with the use of an 'inactive' rather than an 'active' placebo because of the differences in side effects that can occur. Greenberg and Fisher[120] looking at the effect of RCT design on outcome within psychotropic drug trials, point out that "the typical drug trial is transparent because of the use of inactive placebos. The side effect profile associated with virtually every psychiatric medication unmasks both the patients and the research personnel as to who is receiving drug vs. placebo" (p.245).[120] This may not be limited to studies of psychiatric medication but extends to other fields, particularly when outcome is evaluated using subjective factors which may

introduce bias (see further below). Some placebos can also have harmless side effects, such as blackening stools, which are easily detected.

Because the placebo and active treatment usually have different effects, a significant difference between the treatments can be found even in small trials. This means that although the placebo trial can state that the treatment is better than placebo it cannot necessarily evaluate the effectiveness of that treatment in relation to the standard treatment for a condition.[60]

A further issue is the 'placebo effect'. "Placebos are not totally inactive, they are pharmacologically inactive" (Vere p.8)[121] and improvements are commonly found with placebos. In benign prostatic disease, for example, symptom improvements of 32% are not uncommon on placebo, compared to Alpha blockers (48%) and Finasteride (37%).[122]

It is argued by some that the placebo should no longer be part of the 'gold standard' trial. Although placebos have been commonly used because there has often been no effective treatment with which to compare the new treatment, as medical knowledge increases the use of placebos should fall. When a standard treatment is available, it is preferable and ethical to compare this to new treatments.[60] However, placebos are still utilised even when a standard treatment is available. Aspinall and Goodman in a review of published trials of ondansetron for postoperative nausea and vomiting, found that over 2000 patients had been denied effective prophylaxis and over 400 patients who were experiencing symptoms had also been denied effective treatment within the 18 trials.[123] Patients may also be less willing to participate in trials that include a placebo arm.[124]

Bias

Bias includes any aspect or practice within a trial which systematically affects the results leading to an underestimation or an inflation of the efficacy of an intervention.[13] Bias can occur at any stage of a trial from planning, sample selection, execution of the interventions, and analysis, through to the interpretation, reporting and publication of the subsequent results. Although it is

not possible to identify conclusively whether the findings of a study are truly unbiased, certain sources of bias have been identified, as have methods for reducing their effect.[13]

The selection, care and evaluation of patients taking part must not differ between treatments.[15] Selection bias may occur if there are systematic differences in the way in which participants are chosen or subsequently assigned to an intervention within the trial. Randomisation should ensure that the recruiting clinicians and the patients are unable to influence the allocation, however, if eligible patients are excluded because their allocation is known, then selection bias will be introduced. This can also occur when clinicians decide to treat patients with a particular intervention, regardless of random allocation. To prevent such bias, concealed allocation should be included in the design of any trial,[13] ideally by telephone randomisation. Selection bias should not occur if there is true clinical equipoise, where participants are informed of, and consent to, the trial, and when it represents best clinical practice.

Poor management of patients who withdraw, drop out or do not comply with the treatment protocol can also introduce bias. Intention-to-treat analysis can be used to avoid this type of bias.[13] Such problems can also be caused by structural faults in the design of a trial[18] or introduced by the inappropriate use of different RCT designs such as the cross-over trial.[13] The use of a registry or log book to record data on participants and non-participants, giving reasons for non-participation of eligible patients, may increase external validity.[125]

The exclusion criteria for trial entry can be a major source of bias, affecting the validity and generalisability of the results. For example, Schwartz and Fox found that the criteria used in a trial of two psychosocial interventions for multiple sclerosis resulted in only 3% of the initial registry of 1500 patients actually being randomised, with an additional over-representation of patients with the chronic progressive stage of the disease.[126] Similarly, Hunter et al[50] found that of newly diagnosed US oncology patients (44,156), only 9508 were clinically eligible to participate, and of these, only a small proportion (19%) were actually entered

into a trial.[50] McCusker et al found that the results of two lung cancer chemotherapy trials applied only to the 42% of patients who were eligible, because participants were more likely to attend specialist hospital units and have a higher socioeconomic status.[125] The selection criteria used within a trial must be described in detail to allow an assessment of the representativeness and generalisability of the results.[127, 128]

Ascertainment bias can occur when the findings of a study are systematically distorted because treatment allocation is known. To avoid this type of bias, the double-blind trial design can be used to ensure that these groups are unaware which intervention has been allocated[13] (see further below).

McPherson suggests that treatment choice, preference and control may have a therapeutic benefit and because random allocation deprives patients of this benefit, this may lead to a negative estimate of treatment effectiveness.[22] Leventhal et al illustrate how a number of psychosocial and behavioural factors between treatment groups can introduce bias.[129] They found that women in the active treatment arm of a breast cancer prevention trial were more likely to maintain breast self-examination a year after trial participation, while this decreased in the placebo arm. They hypothesise that those in the active treatment group may feel less vulnerable to breast cancer, seeing this task as confirming their healthy status rather than a means of detecting disease.[129]

Failure to standardise the informed consent procedure may also introduce bias, which could in turn change or modify the outcome of a trial.[130] Dahan et al compared the effects of written informed consent on the responses of patients with insomnia to a placebo and found that patients given detailed information about possible side effects experienced more side effects than the control group who received no information.[130] Similarly, a sixfold increase in the number of participants withdrawing from an angina trial occurred within centres which informed patients of a gastrointestinal side effect.[131]

Bias can also occur at the dissemination stage of a trial (publication bias). Studies reporting positive results are more likely to be published in English-language

journals if the findings are statistically significant, whilst negative papers are more likely to be published in German and Japanese journals.[132] Trials with positive results are also published sooner than those with negative results, as is the case for 'potential breakthrough' studies.

A systematic review, that is the evaluation of the evidence from published trials, can be useful, allowing clinicians access to combined results from many trials and up-to-date research. This method is based on the reviewer's personal evaluation and dependent upon access to, and inclusion of, all relevant trials.[15] Meta analysis (where the results of a number of studies are combined to get an overall answer to the research question) is the major quantitative method used. However, any attempt to summarise the findings from a number of trials is problematic and consistency is necessary as trials are likely to differ.[15]

Jadad et al[133] and Moher et al[134] have both developed guidelines to assess the quality of reporting of clinical trials. Broadly, they suggest that the relevance of the research question to clinical practice, the internal and external validity of the trial, the suitability of the analysis and data presentation and the ethical implications of the intervention must all be assessed to establish the quality of reporting. However, one problem with such assessment is that it is based on the quality of the published report, and as Jadad[13] acknowledges, poorly designed but well reported trials may receive a high score, while a well conducted, but badly reported study may receive a low quality score. Kunz and Oxman in their review, conclude that concealed allocation may be a more sensitive measure of bias than current quality assessment scales.[113]

Standards have been developed to improve the level of reporting trials. CONSORT (Consolidation of the Standards of Reporting Trials) provides guidelines to improve the standards of trial publication, both at the submission and final publication stage.[127, 128] Submitted papers must be supplemented with a 21-point checklist to aid reviewers, describing key aspects of the trial necessary to evaluate its validity, for example, details of the methods of allocation and concealment employed. To assist readers, the published report must also include

details of the protocol, assignment, blinding, participant profile and follow-up, flowchart, and details of the data analysis.[127, 128] This statement has been adopted by many high quality journals including the BMJ, The Lancet, Annals of Internal Medicine and JAMA. However, a number of reviews[79, 118, 135] have found that the information provided in many of the trial reports is still inadequate, although this may increase over time as the CONSORT guidelines are increasingly applied.

Validity

Ideally, patients recruited to a trial should be representative of the disease population under investigation. To ensure this, all clinicians involved in the selection process must see a representative group of patients, be willing to randomise a substantial proportion of their suitable patients and agree to accept the random assignments of treatments. Only if a patient does not meet the eligibility criteria should they be excluded from the trial.[15] The generalisability of the trial findings to the target population is referred to as external validity. The internal validity of a trial is dealt with by the use of concealed and random allocation (see further below).

However there are problems associated with achieving external validity. Many recruiting clinicians do not enter all their eligible patients onto trials and this has implications for the realistic estimation of accrual rates and the representativeness and generalisability of trial findings. For example, many were found to overestimate their patient accrual[73, 75] and half of the recruiting clinicians within a number of large scale trials were found not to have entered any of their eligible patients.[47, 75] Similarly, 29% of a sample of Nordic oncologists[136] and 52% of breast cancer oncologists[47] admitted that they had excluded some of their eligible patients from trials. 15% of the recruiting oncologists within one US centre also admitted that they sometimes discouraged participation.[73]

There are a number of reasons for this. It has been suggested that the inherent conflict of taking on the dual role of investigator and physician committed to an

individual patient's health is a barrier for many.[46-48, 136-138] Clinicians may fall into two groups: 'experimenters' who are primarily interested in contributing to scientific information and therapists, for whom the patient is the main focus.[45] Recruiting oncologists have often been found to have such a 'therapist' orientation to their practice[45, 46, 75] and appeared to be deterred because they believed helping individual patients was more important than contributing to research.[46, 75] This ethical dilemma may be one of the main reasons for such exclusions[50] (see further in chapter 1).

Trial design may also be a barrier and it is important to incorporate the recruiting clinician's perspective when designing trials. For example, the design of some oncology trials were often believed to be too rigid and for many recruiters within one US centre, this was their rationale for excluding patients.[73] Many breast cancer clinicians have also been found to have objections to trial design,[45, 49] believing that they would enter more of their patients if trial participation was closer to normal practice.[45] Surprisingly, only a small number were deterred by the practical barriers to recruitment such as difficulty collecting data,[50, 73, 74, 78] the time involved,[73, 74] staff shortages,[74] cost,[73] travel[78] and side effects.[78] However, the majority of these studies have examined those recruiting patients onto oncology trials and it is not known to what extent these barriers are present within trials for non-life threatening conditions.

A number of practical interventions can be employed by trialists or incorporated into the trial protocol to improve the external validity of a trial. For example, Schwartz and Fox suggest targeting potential recruiting clinicians with information and obtaining their prior endorsement of the study may be one way to increase their willingness to allow their patients to participate. Farrell propose that trial campaigns to encourage recruitment should reflect the clinical practice at a local level by translating the recruitment rate so that it has practical meaning for the recruiting clinicians. It must also "offer some sort of kudos or recognition to those willing to participate" (p.1237).[139]

Taylor et al suggest that the recruiting clinicians could be asked to set their own realistic levels of accrual, with a system to support and reward clinicians who meet their targets, or hold accountable those who do not.[75] However, despite the clinicians' right to base their decision on their personal belief about the acceptability of a trial, Segelov argues that such decisions should be documented to ensure that they are not just based on "nonscientific, whimsical feelings" (p.104).[55]

Trialists must become aware of the unique barriers to participation of some groups if they are to achieve an unbiased sample. There is evidence that accrual of women[140] and participants from low income,[141] racial and ethnic groups is lower than for the majority.[59] It has been suggested that to improve the accrual of such groups, the design and recruitment of trials must take into account the social and behavioural aspects of participation.[142] McCabe et al suggest that recruitment strategies should identify the specific cultural needs and barriers to participation of ethnic minority groups. Staff should receive specific training, with nurses having a key role in the identification, education and recruitment of participants from minority groups.[141] Only two studies have examined the attitudes of minority groups to trial participation. These also conclude that trials must be tailored to meet the needs of their target group[58, 143] and recommend that professional and lay representatives of the communities should be involved in the planning of future trials.[143] HIV trial pilot studies similarly suggest that at the design stage, trials should take into account the needs of the target population by understanding individual and community issues.[144-146]

To improve the accrual of those on low incomes, outreach work within the community has similarly been suggested as a way to increase trust and communication, for example by giving public presentations and the setting up of an advisory group that includes representatives from the target population. Collaboration with clinics providing medical care at reduced rates for these populations, improving access and availability of services and employing staff from these population groups has also been suggested to improve accrual.[141]

Providing participants with transportation to clinic appointments may also be effective. Thirty-eight patients in one such study cited travel as their main reason for non-participation and this intervention had the potential to increase accrual rates by 25%.[126]

Information may also be an issue. For example, a small number (34) of the sample of injecting drug users were eligible, but did not enrol onto a phase II clinical trial. Asked for their reasons, many (54%) stated that they were interested in participation but had lost the study information.[147] Many studies suggest that the provision of information before recruitment may increase participation.[142, 148-150] Turner and Sheon in their review, conclude that this must focus on the communication of clinical uncertainty and the potential risks of participation.[151] Others suggesting that trialists must deal with patients' anxieties about taking part[150] by ensuring they have realistic expectations of participation, especially in relation to the benefits of standard therapy.[152]

Outcome measures

To evaluate change, outcome measures are used. Outcome measures can be clinical (impairment), patient based (activities), or use social, demographic and health care utilisation data (participation). An important aspect of the appropriateness of outcome measures is that they must measure change effectively.[153] Measures obtainable from clinical practice can include mortality, case severity, diagnostic tests (e.g. x-rays) and laboratory investigations (e.g. blood tests). Rates of re-treatment, hospital readmission, complications and adverse reactions following the intervention are also used. A common measure to assess the resource implications of an intervention is length of stay.[153]

Patient based outcome measures include questionnaires examining condition specific symptoms and/or bother, quality of life and generic health status. Trials commonly use both a general and a disease-specific health status measure.[154] Qualitative research methods can also be used to evaluate an intervention from the patient's perspective. These can involve in-depth interviews and participant observations within the clinical setting. There are also social, demographic and

utilisation measures, which include mortality, hospital readmission, length of stay, time off work, utilisation of primary care and social/voluntary services.

Depending on their relevance to the design of a particular trial, all or a number of these measures can be used to evaluate an intervention in order to build up a picture of outcome. Primary or secondary outcome measures should be established at the planning stage of a trial. Primary outcomes are those of central interest to the trialists. The number should be limited and although this may vary, it is standard practice to have no more than three primary outcome measures, although in some trials this may be as high as six. Secondary outcomes are the other measures taken within the trial which are not part of the main focus of the trial.[15] Large scale trials that use a small number of simple outcome measures are also being increasingly advocated.[12]

One challenge for future RCTs is to examine disease from the patient's perspective. Patients' views have been neglected in the evaluation of treatments and this methodologically important yet poorly investigated area is the main focus of this thesis. Although clinical outcome can be measured with few problems, the issue of what quality of life questionnaires actually measure is problematic. Thus the validity and reliability of quality of life measures looking at social and psychological well-being are much debated. Quality of life assessment typically involves standardised measures and these can miss issues important for the individual. Although patients are often given the opportunity to indicate the size of the problem they are rarely given the opportunity to rate its actual importance to them.[22]

The evaluation of quality of life is becoming recognised as an increasingly important outcome measure. However, Sanders et al found that less than 5% of all RCTs (1980-97) reported using quality of life measures. Even within cancer trials, where there are expectations of higher levels due to the nature of the condition and the increasing demands of many funding bodies to examine such issues, this was less than 10%.[155] They also found that the quality of reporting quality of life measures is often poor and conclude that standards must be

established to improve the measurement and reporting of quality of life within RCTs.[155]

Wynne suggests that the assumptions made in the evaluation of a therapy and the definition of therapeutic benefit within trial methodology often impose an artificial framework onto the trial findings which may be very different from the trial participants' own beliefs about outcome.[21] The aim should be to give prominence to the characteristics most important to the individual and it has been suggested that an evaluation of quality of life which takes into account individual preferences and values may be more appropriate than standardised measurement.[156] McPherson similarly proposes that quality of life and physical functioning must be assessed from the patient's perspective.[22]

Compliance

From a clinical perspective, patient compliance is a crucial aspect of the success and validity of a clinical trial. Each patient who takes part in a clinical trial is expected to comply with a non-individualised treatment regimen, often not knowing to which treatment they have been randomised in blinded clinical trials. There are also repeated laboratory tests, examinations and interviews and the demands placed upon the individual may be protracted, with many clinical trials lasting for over 2 years. However, there are relatively few studies examining compliance within the RCT.[157, 158]

Patient preferences

Few classically designed trials attempt to take patients' preferences or views into account. Chapter 3 discusses attempts to include patient views. In the section that follows, the rationales for the designs of trials that accommodate patients' preferences are described.

Many eligible patients have a preference for, or do not want to receive one of the treatment options available within a trial. Some refuse to participate in trials for this reason, while others may take part despite such preferences. The outcomes of these groups of patients are rarely examined, although potential participants'

perceptions of the condition, treatment and the trial can affect the internal and external validity of an RCT.[159] As Silverman and Altman acknowledge, the placebo effect suggests that other possible psychosocial influences such as preferences should be examined.[160]

Patients who have strong preferences for a treatment may differ from those without a preference and this may affect the outcome of the trial. For example, those who are allocated to their preference may have a better outcome than others who are unhappy with the treatment they receive.[13] Similarly, patients who prefer one treatment may differ from other participants which may introduce bias into the trial.[24]

Although preferences may be based on a belief that a treatment will be the most effective, quality of life is also an important factor in patients' decision making[24] and may be important for trials where the treatment options have different degrees of impact on patients' lives. For example, in a breast cancer trial with the treatment options of a lumpectomy or mastectomy, preferences are likely to vary considerably between individuals. Such treatment options may only seem comparable to relatively few patients eligible to participate in the trial.[159]

Thus, preferences may affect accrual. Although the recruiting clinician may believe that the treatment options available within a trial are equally effective on the evidence so far, the decision to participate is left to the patient and this may depend on their preferences for one treatment over another.[159] Barofsky and Sugarbaker found that willingness to participate in three skin cancer trials was dependent upon patient perceptions of the trial treatment options. They suggest that differing rates of trial accrual may be due to the disparity between patients' prior experiences and expectations and the treatments available, concluding that the influence of these factors on patient accrual and retention should be addressed in the design and implementation stage of trials.[161]

Preferences can also have implications for the trial findings. For example, Berry et al found a range of treatment preferences among a sample of rheumatology patients (n=60) taking part in a crossover double-blind drug trial. The greatest

difference between the two experimental groups occurred in patients who wanted improved mobility from the treatment, despite any side effects they experienced.[162] Patients' motivations for following a treatment may also be influenced by their initial preferences, for example, when an intervention involves self monitoring or dietary changes.[109] It has been argued that where at least one of the trial interventions are participative, motivation will be equally distributed across intervention groups because only patients who receive informed consent and agree to be randomised are included.[109] However, such patients may still have strong preferences, agreeing to participate only because there is a chance they will be allocated to their preference or because it is their only chance of receiving the experimental treatment. If such patients are not allocated to their preference, this may reduce their motivation and lead to biased estimates of treatment effectiveness.[109]

Kassirer identifies seven circumstances where preferences are likely to vary widely or are 'utility-sensitive': where the potential outcomes of treatments are very different; where possible complications and repercussions resulting from the treatments are very different; when decision-making involves choosing between short and long-term outcomes; when one of the treatments has a small chance of resulting in a grave outcome; where the differences between treatments are minimal; when a patient is averse to risk taking; or when a patient places their hopes on one possible outcome.[163]

It has been argued that in such cases randomisation is not always appropriate and may itself lead to bias. Trials do not replicate what usually happens in everyday life, where treatment is individualised,[164] and specifically the process of random allocation means that patients are deprived of choice, preference and control over treatment which may have a therapeutic benefit. In theory then, randomisation itself may lead to a biased estimate of a treatment's effectiveness.[22]

Alternative designs could be considered for trials which will be demanding for participants or where patients are likely to have strong preferences for one of the

treatments.[109] Zelen's design, the comprehensive cohort and Wennberg's design, all take patients' preferences into account. These trial designs include at least one group of participants who have been allocated to their preferred treatment and are referred to as preference trials.[13]

Zelen model of randomisation

Within a Zelen designed trial, patients who are eligible to participate are initially randomised to one of two groups. The first group are a 'do not seek consent' (control) group and are allocated to the standard treatment. Patients within the second group are asked to give informed consent to participate in the trial and receive the experimental treatment. If they agree, then they receive this treatment, or they can decline this and receive the standard treatment. In a modification of this design, Zelen suggests that patients in this second group can be given the opportunity to receive their preferred treatment. The analysis of such a trial compares the outcome of patients allocated to the control group who received the standard treatment with the second group, regardless of whether they received the standard or experimental treatment.[23]

The double randomised consent design is a modification of the Zelen design, which attempts to deal with the ethical problem of not informing participants that they have been randomised to the standard treatment. Here participants are told to which group they have been allocated and given the chance to change to the alternative treatment group.[13]

Zelen believes the main benefit of this design is that it does not compromise the doctor-patient relationship, as the recruiting clinicians only need to discuss one of the treatment options and do not have to mention random allocation. From the patient's perspective, this method simplifies the decision making process since patients know which treatment they are agreeing to receive.[23] This approach also ensures the participation of the majority of eligible patients, allowing the evaluated effect of the experimental treatments to be generalised.[13] This design was used within the National Surgical Adjuvant Project for Breast and Bowel Cancer Trial.[159] By randomising before they obtained patients' informed consent

to participate in the trial, accrual increased sixfold. However, this introduces the ethical problem of not giving such patients informed consent prior to randomisation (this has been discussed in more detail in the previous chapter).

However, Zelen also points out that the analysis of such trials may not be able to detect possible treatment effects and patient characteristics if these are related to patient preferences.[23] It has also been argued that where participation is based on preferences the sample will not be representative of the target population. Comparing the outcomes of randomised and non-randomised groups is also likely to introduce uncontrolled confounders and hence problems of validity.[160]

Comprehensive cohort design

The comprehensive cohort design is effective where a large number of eligible patients refuse to participate because they have strong preferences for one of the treatments available within the trial.[13] Using this design, patients are initially asked to give their consent to be randomised and those who agree are randomised to one of the trial interventions. Patients who do not agree to be randomised, receive their preference and are followed as if they were within a cohort study. All participants are followed-up, regardless of whether they were randomised or not and the outcomes of the trial and cohort participants are then compared. The main limitations of this approach is the difficulty of determining whether the results from a small number of randomised patients can be applied to the target population[160] and in establishing whether any outcome differences between the groups are real or due to differences in baseline characteristics between the two groups.[13]

Wennberg's design

Here eligible patients agree to be randomised to either an 'RCT group' or a 'preference group'. Those randomised to the preference group are given the option of choosing which intervention they receive, while the RCT group are randomly allocated to one of the interventions. The outcomes of the two groups are then compared and this is used to estimate the impact of preferences on outcome.[13]

Clinician-preferred design

It is often difficult to achieve a consensus among clinicians as to the appropriate eligibility criteria for certain trials, hence many clinicians are often reluctant to randomise and enter their patients onto trials.[164] In response to this problem, the clinician-preferred treatment trial design has been proposed. Using this method, eligible patients are assessed using fixed criteria to establish whether clinicians would be likely to have a treatment preference and if this is the case, these patients are excluded. A panel of 2-4 clinicians then individually assesses those remaining, and only if there is disagreement within the panel is informed consent sought and the patient randomised. They are subsequently assigned to the clinician preferring this treatment allocation during the patient's screening process. However, because this design restricts participants to a specific group of patients, the applicability of the trial to the patient population is problematic.[164]

Other approaches

Other approaches have also been suggested to address this issue. Widder's solution would be to ask patients to consider why they want treatment and what they want or expect their treatment to achieve before entering a study. Only when patients' aims are in concordance with the aims of the trial should they take part.[165] Alternatively, Thornton suggests that one way to address patients' preferences within trials is for patients to be involved at the design and planning of trials and for their preferences to be integrated at this stage.[166]

Preference trials are seldom used, although with the growth of consumer participation in decision making this method is likely to be increasingly used.[13] A number of preference trials have been carried out,[167-171] although relatively few involving surgical procedures. An exception is the trial by Henshaw et al[167] to evaluate the acceptability of medical abortion and vacuum aspiration. Just over half (54%) of the eligible women willing to participate (n=363) had no preference and agreed to be randomised. Those who did not want to be randomised were allocated to their preference: medical abortion (20%) and vacuum aspiration (26%). A self-completion questionnaire assessing the acceptability of the

treatment found that 22% of those randomised to a medical abortion would choose a different procedure in the future compared to only two of the women allocated to vacuum aspiration. Henshaw et al suggest that it would not be possible to obtain this type of information without a trial design that took preferences into account.[167]

However, there are problems associated with the use of preference trials. King et al[170], carried out a pilot preference trial to evaluate counselling in general practice. Overall, the majority of patients (particularly those with higher psychiatric scores), were allocated to the counselling intervention. The authors speculate that the recruiting GPs may have been influenced by the severity of the patients' illness and directed their preferences. This was confirmed by many of the GPs who remarked that they may have influenced patients' choices by suggesting that counselling may be beneficial.[170] Angell similarly notes that although the Zelen method may increase accrual, this may be the result of clinicians' withholding or colouring information in favour of the treatment to which the patient had been allocated.[159]

Preference trials have been considered and rejected for a number of controversial studies. In a breast conservation trial where patients would be randomised to one of two types of surgery, mastectomy or lumpectomy (which may provoke strong preferences), the working party rejected the Zelen method of randomisation. They believed it would be unethical to seek informed consent from only one group of patients. Legal action was also a consideration. If a patient who received a mastectomy later finds out that they had taken part in a clinical trial and discovered that they had been denied the more conservative treatment (lumpectomy), they would be in a position to sue.[172] The Zelen approach was also suggested for a number of paediatric trials. However, this was seen as only a partial solution for a trial of critically ill babies with acute respiratory failure because participants would receive less information, when qualitative research had concluded that clearer information was required prior to randomisation.[173] Similarly, Levene et al concluded that the trial design proposed by Zelen is no

alternative in trials of premature infants because of the legal requirement to obtain parental consent. They believe that where early entry is required, informed consent should be a continuous process, with parents provided with further written and oral information after randomisation. They recognise that in these trials consent is obtained before parents are fully informed.[174]

A dominant feature of medicine is choice and the need to communicate the associated probabilities. Silverman and Altman suggest that misconceptions about probability may be an important aspect of preferences and thus patients must be protected from exaggerated claims about new treatments.[160] The importance of patient preferences varies with the condition, but may be particularly important for conditions such as benign hyperplasia of the prostate, where there is not only a choice between treatments, but a decision about whether treatment is necessary.[22]

So far trialists have been reluctant to involve patient groups in the design of trials. However, patients may prefer different outcomes from those imposed by trialists. For example, in the development of a trial for young people with sickle cell disease, Prestifilippo et al[56] found that although morbidity was the main clinical outcome, patients did not see this as the most important criteria for assessing trial outcome.[56] Naylor and Llewellyn-Thomas[175] suggest that patients and the public should be involved in trial planning and be able to indicate the level of benefit they want from a 'new' treatment, given the known side effects from this treatment that may occur.[175] They believe that the probability trade-off technique could be used to ensure that patient autonomy and the principles of informed consent are incorporated, even though this approach means adding another stage onto the design of a trial.[175]

Conclusion

The focus on the RCT as the only unbiased method to evaluate a medical intervention has led to an increasing awareness of the problems of attaining the required level of precision, validity, and the feasibility of this approach. However, textbooks and reports in journals focus on the design, methods and

results of trials,[15, 106, 176] suggesting that each decision in the planning and design of a trial, from selecting the intervention, the population, and the aims of the trial, occurs in isolation and according to standard rules. The possible impact of these decisions on patients is often ignored and such decisions may influence the behavioural dynamics and thus affect the internal and external validity of a trial.[129] The following chapter examines the experience of trial participation.

Trial Participation: patient perspectives

Introduction

In this chapter, research relating to the publics' and patients' perspectives of being involved in RCTs will be considered. Studies have primarily been undertaken from the perspective of trialists, often using hypothetical trial scenarios with a variety of lay or potential trial populations with the ultimate aim of improving accrual within future trials. Studies that explore the experience of participation have predominantly used structured questionnaires to examine motivation, satisfaction and barriers to recruitment. The assessment of the informed consent procedure within trials has also been the subject of many studies, often evaluating effectiveness using recall and recruitment rates. Only recently and in a few studies has there been an assessment of the perspective of actual participants: their attitudes towards, their experience of and motivation for taking part in a clinical trial.

Attitudes to participation

Hypothetical participation

Many studies have used hypothetical scenarios to determine willingness to participate in trials. These often attempted to assess general attitudes to trial participation by examining the attitudes of the public.[99, 177-180] Others have focused on potential trial populations of patients[49, 124, 142, 181, 182] and specific treatment groups, for example, paediatric and psychiatric populations[148, 149] or racial and ethnic groups often underrepresented within trials.[58, 143] Many have been used to assess the feasibility of trials for particular conditions which potentially present specific ethical, methodological or accrual difficulties. From the perspective of the trialists, these studies aim to gather information to improve the feasibility of, and accrual rates to, these proposed trials by presenting hypothetical scenarios to their respective populations, particularly in the areas of

HIV[144-147, 183-185] and oncology.[49, 142, 150, 186] A summary of these studies can be found in tables 1 and 2 below.

Table 1: Surveys, structured and unstructured schedules used to explore hypothetical participation

Author	*Population assessed*	*Sample size*	*Purpose of the study*	*Outcome measurements*	*Main results*
Kemp et al[178]	UK Lay population	(1022)	General attitudes - oncology trial scenarios	Structured survey	Participation -63% Trust-88%
Mackillop et al[179]	Lay population (Canadian)	(400)	General attitudes- oncology trial scenarios	Structured survey	Participation -50% Altruism-63%
Millon-Underwood et al[143]	US African-American population	(220)	General attitudes to oncology trials	Structured survey	Participation-75% Trust-20%
Saurbrey[182]	Danish in-patients	(114)	General attitudes- a range of trial scenarios	Structured interviews	Participation- 98% Trust-86%
Bevan et al[181]	UK outpatients	(119)	General attitudes-a range of trial scenarios	Structured interviews	Participation- 70% Altruism-57% Personal benefits-42%
Cassileth et al[177]	US Patients and the public	Patients (186) Public (107)	General attitudes to trial participation	Self-completion questionnaire	Participation- 71% Altruism-55% Personal benefits-52%
Gerrard et al[149]	French community psychiatric population	(609)	To evaluate the potential impact of informed consent regulations	Postal questionnaire	Participation- 50%
Mettlin[142]	US population who had been screened for cancer	(576)	A feasibility study for an oncology trial	Postal questionnaire	Participation- 77%
Slevin et al[150]	UK oncology patients	(75)	General attitudes- oncology trial scenario	Self-completion questionnaire	Participation- 42% Personal benefits-83% Altruism-75%
Llewellyn-Thomas et al[186]	US colorectal cancer patients	(60)	Presented with an actual clinical trial protocol	Self-completion questionnaire	Participation- 25
Autret[148]	French parents	(541)	To evaluate the potential impact of informed consent regulations- paediatric scenario	Self-completion questionnaire	Participation- 21% Personal benefits-44% Altruism-67% Trust- 52%
Flanery et al[99]	US students	Medical (57) Mathematics (67)	Presented with a 'typical' consent form to (hypothetically) participate	Structured questionnaire- multiple choice	Personal benefits-49% Altruism-88%
Alderson[49]	UK clinicians and breast cancer patients and screened women	Clinicians (40) Patients (50) Screened women (93)	Ethics	Interviews with clinicians and patients. Postal survey of those screened	Altruism, personal benefits important motivations within all groups
Corbett et al[180]	UK lay and medical population	Public (50) Medical - secretaries (25) Students (25)	Informed consent	Comparison of different way of providing informed consent	Non-participation due to adverse effects of treatment-25%

Welton et al[124]	UK general practice	Post-menopausal women (436)	Recruitment	Interviews	Altruism-26%
Roberson[58]	Minority groups in New York	(28)	General attitudes to trial participation	Qualitative telephone interviews	Altruism Mistrust

Table 2: Surveys and structured schedules used to explore hypothetical participation within target populations for HIV vaccine trials

Author	*Population assessed*	*Sample size*	*Purpose of the study*	*Outcome measurements*	*Trial information*	*Main results*
McQueen et al[183]	(US) Gay and bisexual men	(1071)	Feasibility study-HIV vaccine trial	Structured interviews and self-completion questionnaires Ranked scales	A brief statement explaining the vaccine and the trial	Participation- 37% Personal benefits- 37% Altruism-40%
Bartholow[144]	Men who have sex with men (US)	(1267)	As above	As above	A brief statement followed by a fuller disclosure of possible risks of participation	Initial participation- 81%, dropping to 21%
Douglas[146]	Men who have sex with men (US)	(1660)	As above	As above	No details	Altruism-94% Distrust-58%
Jenkins[184]	Thai health care workers	(255)	As above	Survey and open-ended responses to a questionnaire and focus groups	No details	Concerns about safety and discrimination
Wiley et al[185]	Men who have sex with men (US)	(371)	As above	Structured self-completion questionnaires	No details	Participation- 62% (later dropped by half)
Vlahov[147]	(US) mainly Black (94%) population of HIV seronegative injecting drug users	(375)	As above	Structured interviews and self-completion questionnaires – willingness to participate rank on a scale	A fuller disclosure of possible risks of participation	Initial participation- 85%, dropping to 27%
Gross et al[145]	(US) Gay and bisexual men	(630)	As above	Structured self-completion questionnaires	No details	17% 'very interested'

Overall, these studies found favourable attitudes towards hypothetical trial participation among the general public, ranging from 48%-75% agreeing to participate.[143, 177-179] Many (70%) would still contribute, even if this meant undertaking dietary changes (77%) or taking vitamin supplements (73%).[142] Perhaps surprisingly, 40% would participate even when one of the treatment options involved amputation.[178] These studies suggest, then, that a large proportion of the public is willing to participate in clinical trials- in theory at least.

Three studies suggest that patient groups, with rates of 50%,[149] 70%,[181] and up to 98%,[182] were also willing (hypothetically) to take part in trials relevant to their condition.

However, lower levels of willingness to participate were found in response to two oncology trials[150, 186] a gynaecology trial,[124] and a paediatric trial.[148] Less than half of two samples of oncology patients would agree to participate.[150, 186] Similarly only 21% of French parents (541) surveyed would agree to participate, but the majority (74%) would not allow their children to take part.[148] However, these findings are not surprising, given the potentially life threatening (cancer) and emotive (paediatric) trials these studies examine.

Willingness to participate varied amongst the target populations for HIV vaccine trials. McQueen et al found 37% of gay and bisexual men were 'definitely' willing to participate,[183] although Gross et al found only 17% very interested in taking part.[145] Willingness to participate was often related to the amount of information these men received about such trials. Three studies initially found high levels of willingness, ranging from 62%,[185] up to 85%.[144, 147] However, after receiving additional detailed information about what participation in such a trial would involve, this dropped by almost half (no figure given)[185] and to as low as 21% in one study.[144] For example, once injecting drug users were informed that the vaccine might lead to a false positive HIV test result, willingness to participate dropped by almost half to 47%, and to 27% when they were told that the vaccine might contain a piece of the virus.[147] Such trials clearly contain a number of particularly difficult issues for patients to deal with.

Actual participation

A fundamental problem with many of the studies above is their reliance on attitudes to *hypothetical* (not real) trial participation. As Gerard et al acknowledge, although 50% of their sample were willing to participate in clinical trials, intention may be different from actual participation rates.[149] Those who have taken part in a trial may have a real and distinct difference of opinion compared to those whose responses are based on speculation.[178, 182]

Much of the literature evaluating patient participation in clinical trials is concerned with improving recruitment, by examining the 'mechanics of the process' and identifying methods for achieving a low refusal rate in future trials. Little is known about why patients decide or refuse to participate in clinical trials. "Do they see themselves as willing volunteers entering clinical trials to help both themselves and humanity or do they feel that they are victims, being used as guinea pigs in an experiment over which they have little control?"(pp.1270).[150] Only recently and in a few studies has this been seen from the perspective of actual participants: their attitudes and motivation for taking part in a clinical trial.

Surveys and structured schedules have been used to explore participation within large-scale heart disease trials,[187-189] phase I oncology trials,[190, 191] paediatric trials,[97] UK out-patients,[181] a gynaecological trial[105] and an arthritis trial.[192] These studies have been summarised below within table 3.

Table 3: Surveys and structured schedules used to explore participation

Author	*Population assessed*	*Sample size*	*Purpose of the study*	*Outcome measurements*	*Main results*
Daugherty et al,[191]	US oncology patients prior to participation in a range of phase I cancer trials	(27)	Motivation and perceptions of participation	Structured interview schedules with additional open-ended questions	Personal benefits- 100% Trust- 75%
Hudmon et al[190]	US oncology patients who had completed a phase I colon cancer trial	(64)	Motivation and perceptions of participation	Postal survey Multiple choice questions	Altruism- 95% Personal benefits- 95%
Mattson et al[187]	(US) Asprin Myocardial Infarction Study (AMIS) trials Beta-blocker Heart Attack Trial (BHAT)	(398) (1503)	Retrospective study of participation	Structured questionnaire interviews with additional open ended questions Postal questionnaire	Personal benefits- 84% Problems with transport- 11%
Henzlova et al[188]	(US) chronically ill middle aged and elderly participants in a long-term heart failure trial	(3522)	Perceptions of participation	Survey- structured questionnaire *Not anonymous*	Trust-31% Personal benefits- 25% Altruism-32% Problems with transport- 21%
DeLuca et al[189]	(US) participants within 12 cardiovascular trials	(172)	To identify sociodemographic predictors of informed consent	Structured interviews	Personal benefits- 88% Altruism-79% Pressure to participate-63%
Harth and	Parents who had volunteered their	(68)	To identify sociodemograph	Structured interviews with additional open-	Personal benefits- 90%

Thong[97]	child onto an asthma drug trials (Australia)	(42 non-participants)	ic predictors of informed consent	ended questions	Altruism-100% Trust- 48%
Lynoe et al[105]	Women after participation in a Swedish gynaecological trial	(43)	To assess recall of informed consent	Postal survey based on the Declaration of Helsinki	Altruism-56% Personal benefits-35%
Bevan et al[181]	UK out-patients who were current or previous trial participants	(66)	General attitudes-a range of trial scenarios	Structured interviews	Altruism-62% Personal benefits-38%
Hassar and Weintraub[192]	Participants in an arthritis trial	(17)	Knowledge of the trial and reasons for participating	Structured self-completion questionnaires	Personal benefits-94% Altruism-88%

Qualitative in-depth interviews were carried out with participants predominantly within breast cancer trials,[83, 193] oncology trials,[194-197] HIV drug trials,[198, 199] a paediatric trial,[173] a prostate trial[200] cystic fibrosis[201] and a herpes trial.[68] Longitudinal studies have been carried out by three of these studies.[196, 197, 201] Additionally, Jayne Harrison describes her personal motivation to participate in a breast cancer trial.[202] These studies have been summarised below within table 4.

Table 4: Qualitative and semi-structured schedules used to explore participation

Author	*Population assessed*	*Sample size*	*Purpose of the study*	*Outcome measurements*	*Main results*
Charles et al[193]	Canadian women in breast cancer trials	(20)	Decision making	Qualitative in-depth interviews	Personal benefits Trust
Jensen et al[83]	Danish women in breast cancer trials	(34)	Evaluation of informed consent	Qualitative in-depth interviews	Altruism -26% Personal benefits-24%
Cox and Avis[196]	UK participants in phase I and II oncology trials	(7)	The psychosocial aspects of participation	Longitudinal semi-structured interviews before and after completion	Personal benefits-hope Trust Some altruism
Blair et al[201]	UK participants in a phase I safety trial of gene therapy for cystic fibrosis	(16)	The psychosocial aspects of participation	Longitudinal semi-structured interview before and after completion. Health measurement scales	Personal benefits-56% Trust-25%
Stetz[197]	Participants with advanced liver cancer - Their partners-	(24) (16)	The experience of participation	Longitudinal semi-structured interview before and after completion	Personal benefits-survival, hope
Tabak[194]	(Israel) oncology and vascular patients	Oncology (23) vascular (20)	To assess decision making	Structured interviews before participation	Trust
Rodenhuis et	Participants within a	(10)	Motivation to	Interviews	Hope

al.[195]	Dutch Phase I oncology trial		participate		Trust
Snowdon et al[173]	UK study of parents who had agreed to the participation of their newborn child with acute respiratory failure in a clinical trial	37 (21 couples)	Understanding of randomisation	In-depth interviews	In only half of the interviews (12) did one parent believe their allocation was based on chance
Featherstone and Donovan[200]	Participants in the ClasP prostate trial	(20)	Understanding of randomisation	In-depth, semi-structured interviews	Many recalled randomisation Lay interpretations of the concept
Tindall et al[198]	HIV positive men one week before taking part in an HIV drug trial (Australia)	(113)	To examine informed consent	Self-completion structured questionnaires	Trust- 88%
Ryan[199]	HIV positive men participating in AIDS clinical trials and HIV phase I trial (Australia)	(16)	The experience of participation	In-depth semi-structured interviews Participant observation	Confidentiality 'watching sick people' The clinic setting
Searight and Miller[68]	Patients after participation in a herpes trial. All White, well educated and predominantly female.	(14)	From the perspective of informed consent	Semi-structured interviews	Altruism Personal benefits

The majority of studies have examined participation within oncology trials.[83, 190, 191, 193-197] paediatric trials[97, 173] and HIV trials[198, 199] It can be seen in tables 3 and 4 that the main focus, as with the hypothetical studies, has been an examination of participation within trials that present trialists with specific ethical problems. For example, five such studies have considered Phase I trials[190, 191, 195, 196, 201] where the aim is to determine the maximum dose tolerated and the toxicity of new drugs. Traditionally, a drug is administered at low levels, followed by a succession of dose increases. Hence, the chances of receiving any personal medical benefits from participation is small while the toxicity of the treatment may be high.[191] Similarly, because of their inability to provide fully informed consent,[30] the use of children in medical research is a much debated ethical area.[69, 97] Parents are expected to make important, complex and possibly life-changing decisions about their unborn or newborn child.[173]

A number of studies examined participation within Phase I trials. Two US studies used structured schedules, Hudmon et al in a postal survey,[190] while

Daugherty et al included additional open-ended questions within the interview schedule.[191] Daugherty et al interviewed patients (27) before participation in a range of cancer trials,[191] while Hudmon et al examined perceptions after completion (64) of a colon cancer trial.[190] Two UK studies were longitudinal in design. Blair et al examined a phase I safety trial of gene therapy for patients (16) with cystic fibrosis,[201] while Cox and Avis examined participants (7) within phase I and II cancer drug trials. Both used semi-structured interview schedules before and after completion of the trial and in addition, Blair et al employed a number of health measurement scales.[201]

Oncology trials were also explored by a further four studies. Participants in breast cancer trials were interviewed by Charles et al[193] (Canadian women) and Jensen et al (Danish women).[83] Additionally, Jayne Harrison describes her personal motivation to participate in a breast cancer trial.[202] A longitudinal qualitative study of trial participants (24) with advanced liver cancer and their partners (16) was carried out by Stetz,[197] while Tabak (Israel) interviewed oncology (23) and vascular patients (20) who had been offered experimental treatment.[194]

Four US studies explored the motivation and satisfaction of participation in large-scale heart disease trials. Mattson et al examined survivors of a myocardial infarction taking part in two randomised, double-blind, placebo-controlled trials. Within the Aspirin Myocardial Infarction Study (AMIS), participants (398) were interviewed using a structured questionnaire with additional open-ended questions. These results were then used to inform a postal questionnaire sent to patients (n=1503) within the Beta-blocker Heart Attack Trial (BHAT).[187] The focus for Henzlova et al was a survey of chronically ill middle aged and elderly heart patients (3522) participating in a long-term heart failure trial[188] and DeLuca et al also interviewed participants (172) within a range (12) of cardiovascular trials.[189]

Paediatric trials were examined by three studies. Harth and Thong examined the attitudes of parents (68) who had volunteered or had decided not to volunteer

(42) their child in a randomised, double blind, placebo controlled asthma drug trial in their 1990 study.[97] Their 1995 study examined a similar group of parents (62), although this study was mainly concerned with issues of informed consent.[69] Both samples were interviewed using a structured questionnaire containing additional open-ended questions.[69, 97] Snowdon et al in a UK study, carried out qualitative interviews with thirty seven parents (21 couples) who agreed to the participation of their newborn child with acute respiratory failure.[173]

A range of other trials has also been examined. Two Australian studies examined participation in HIV drug trials.[198, 199] Tindall et al interviewed HIV positive men (113) one week before taking part in an HIV drug trial[198] and Ryan similarly carried out in-depth interviews with current or recent participants in AIDS clinical trials (16). Additionally, trial nurses (12) were interviewed and a participant observation of one HIV phase I trial was carried out.[199] Qualitative methods were also used by Searight and Miller who interviewed participants (14) after their completion of a herpes trial.[68] Lynoe et al in a Swedish study carried out a postal survey of women (43) after participation in a multi-centre gynaecological trial.[105] Bevan et al[181] carried out structured interviews with 66 UK out-patients who were current or past trial participants,[181] while Hassar and Weintraub employed structured self-completion questionnaires which included true/false and multiple choice questions with participants (17) in an arthritis trial.[192]

Motivation to participate

Both the quantitative, structured studies (see table 3) and those employing qualitative research methods (see table 4) have examined participants' motivation to take part in a trial. The studies examining the hypothetical motivation to participate are also reported here (see tables 1 and 2). They identify altruism, trust in recruiting clinicians and an expectation of receiving personal benefit as the main personal motivations for taking part in a trial. There was

often an overlap, with most patients motivated by a combination of these reasons.

Altruism

A feeling of altruism, that is, the desire to help others and the progress of science, was an important motivation among participants. Within Phase 1 trials, almost all the colon cancer patients (95%) believed that altruism was a very or extremely important aspect of their participation.[190] This was reflected to a lesser extent in the qualitative findings of Cox and Avis[196] and similarly, over half of the participants (56%) in the gene therapy trial believed they would not benefit personally.[201] Helping others was cited by almost all parents (98%),[97] arthritis patients (88%),[192] out-patients (62%),[181] and over half of the participants in a gynaecological trial (56%).[105] Many were motivated by the belief that their participation would contribute to medical research. This included all the parents,[97] the majority in a range of cardiovascular trials,[189] just over a quarter of breast cancer trial participants[83] and the majority of the 14 participants within a herpes trial.[68] Within a trial of social support in pregnancy, altruism was reported to be the main reason women agreed to participate.[203]

The high level of altruism displayed by participants within Phase 1 trials may also be linked to the nature of the trials and the seriousness of their condition. When the drug did not work or only worked for a short time, anger and resignation often replaced the (UK) oncology patients' initial hope. These participants were left to face death and in an attempt to find a positive meaning for taking part, they hoped they had helped the clinicians and future patients.[196] Similarly, Jayne Harrison in her personal account, cites altruism and wanting to contribute to the clinical understanding of breast cancer treatment as her main motivation.[202]

Altruism was also the main (hypothetical) motivation among UK out-patients generally (57%),[181] a UK general practice sample of women (26%)[124] UK oncology patients (75%)[150] and the Canadian public (42-63%)[179] in response to a range of oncology trials. Qualitative telephone interviews with minority groups in the US

also identified altruism as the main incentive for participation.[58] Among women with breast cancer (92%), and screened women (50%), the main motivation for (hypothetical) participation would be to help others. This was also the case for breast cancer clinicians, whose main motivation was to help others (82%) and to increase knowledge about this condition (92%).[49]

A specific desire to help future patients was the main reason cited by US cardiology and cancer patients and the public (77%),[177] French parents (67%),[148] and almost half (40%)[183] and nearly all (94%)[146] of two similar populations of men asked to participate in HIV vaccine trials. Macqueen et al[183] observed that those who were definitely willing to participate in HIV vaccine trials tended to use language reminiscent of a war effort, describing AIDS as an 'epidemic' and the 'virus'. Thus, willingness to participate was often in response to the loss or possible loss of loved ones to AIDS (12%), and out of a sense of duty to the community (11%).[183]

Increasing scientific knowledge was a significant motivation for French parents (53%)[148] and for US patients and the general public (69%).[177] To a lesser extent this was also a motivation among UK out-patients,[181] UK oncology patients,[150] the Canadian public[179] and gay and bisexual men.[183]

A small number of studies question the importance of altruism. For example, Kemp et al found that few (5-10%) of their UK population sample who were willing to participate in a range of oncology trials would do so for altruistic reasons, with the majority placing their trust in the clinicians.[178] Similarly, only 22% of the sample of African-Americans cited altruism as their motivation.[143] Both studies examined attitudes to cancer trials and it may be that the primary motivation for participating in this type of trial would be to benefit personally. Within actual trials, only 32% of participants within one heart failure trial (although this was still the main motivation amongst this group)[188] and none of the respondents within a range of US oncology trials referred to altruism as their main reason for participating.[191] They suggest that the chronic or life threatening illnesses of such groups may mean that personal benefits are more important.

However, altruism was a common motivation to take part in a number of similar oncology trials.

The importance of altruism as a motivation to participate is variable. This may be associated with the different methodologies employed by these studies. Surveys and structured schedules used to examine both actual and hypothetical participation found high levels of altruism ranging from over half (56%) up to 100%. Hypothetical studies using qualitative methods also found high levels of altruism; however, such motivations are perhaps to be expected from what were predominantly lay groups where their responses are based on speculation. In contrast, this was a weak motivation within only a few studies examining actual participation using qualitative methodologies to examine the experience of participation.[83, 193, 196, 201]

Trust

For patients with a life threatening condition, trust in the clinician often constitutes an integral part of their decision making.[194] Two thirds of participants in US oncology trials[191] placed their trust in the research oncologist, the referring clinician or the institution, and the majority (89%) of colon cancer patients similarly believed that there was no better option than to participate in the trial.[190] Qualitative interviews with oncology trial participants also found this to be an important motivation for the majority.[193, 196] They expected their clinicians to be responsible for decision-making, in the belief that they did not have the knowledge to make such decisions.[193, 196]

Tabak suggests that for cancer patients, the life threatening nature of their condition may create a special behaviour pattern that overcomes any reluctance to agree to experimental treatment. These cancer patients were under significant pressure to participate in experimental treatments and their recruiting clinicians confirmed that few made independent decisions, participating either from lack of choice or based on trust in the recruiting clinician.[194]

This may also be the case for other groups of patients with life-threatening conditions, for example, HIV, cystic fibrosis, heart disease and paediatric trials.

The majority of HIV positive trial participants (88%),[198] and a quarter (4) of patients within the gene therapy trial for cystic fibrosis,[201] believed that their clinician always acted in their best interest. Any concerns were mitigated by the general belief that the clinicians would not put them at risk.[201] Within two heart disease trials, trust in their clinician (63%),[189] and the recommendation of the primary physician (31%),[188] were the main motivations. The majority of parents also placed their 'trust in the hospital' (48%), frequently volunteering their children because they 'liked the people conducting the trial' (72%).[97]

Trust in their clinician or clinicians generally, was an important factor for many who were willing (hypothetically) to participate. The majority of a UK population survey (88%),[178] Danish patients (86%),[182] and half of French parents (52%)[148] had high levels of confidence in their clinicians. A UK lay sample often believed that the 'doctor knows best' in response to a range of hypothetical oncology trials (69-70%).[178] Similarly, Macqueen et al found that those definitely willing to participate in HIV vaccine trials appeared willing to place their trust in the researchers.[183] However, only a small number within an African-American sample (20%)[143] and a Canadian general population sample (5.2%) would participate for such reasons.[179] The African-American sample were sceptical of the effectiveness of cancer treatments[143] and the Canadian sample[179] were predominantly motivated by altruism.

An association between socio-economic status and willingness to trust the recruiting clinician has been identified. Kemp et al, in a large scale survey of a UK lay population, found that those who were older (60-70yrs) and from lower socio-economic groups were more likely to agree, while younger groups (25-34yrs) or with a higher socio-economic status were more likely to refuse, preferring to choose their own treatment.[178]

The perceived expertise of the recruiting clinicians may also play an important role in recruitment. Half (51%) of the UK oncology patients wanted the clinician to allocate them to a treatment[150] and 70% of US patients and the public, similarly believed or were unsure if 'doctors know privately which one of the

investigative treatments is best'.[177] Over half (58%) of Danish patients believed that ethics committee approval conferred extra protection.[182] Thus, when participation is motivated by the chance to receive the best treatment, the clinicians' recommendation of the trial may be interpreted by patients as equivalent to the clinician recommending the best treatment.[178]

Personal benefits

Physical improvement as a result of receiving the new experimental treatment was a widespread expectation. This was an important motivation for all (100%)[191] and almost all (95%)[190] of the participants in a range of Phase 1 trials, even though the actual chances of receiving any personal medical benefits from such trials was small.[191] This is confirmed by two qualitative studies which also found that the majority of participants within a range of Phase I trials had unrealistically high expectations of the experimental therapy.[196, 201].

Few participants and only within two US heart disease trials were motivated by access to free medical care, ranging from 1.4[188] to 11%.[187] An expectation of receiving better health care was an important motivation to hypothetically participate among UK out-patients (42%),[181] a sample of US patients and public (52%)[177] and for up to 62% of the Canadian public.[179] Such personal benefits as receiving treatment from a specialist (83%), increased monitoring (80%) and receiving greater information about their condition (75%) were also important for UK oncology patients.[150] To increase their chances of obtaining the best care was an important motivation for women with breast cancer (43%) and screened women 40%. Interestingly, a sample of breast cancer oncologists similarly believed that trial participation would improve their access to the best care (67%).[49]

After participation, improved outcome was often attributed to the trial and the experimental treatment. The majority of parents whose babies had received the 'new' treatment for acute respiratory failure believed that this was responsible for their child's survival and they were 'lucky' to receive this treatment.[173] Of those recruited to heart disease trials, many believed that they had received

emotional (62%) and physical (56%) benefits[188] and often ascribed their improvement to their allocated medication (43%), with the trial benefiting their general (24%) and cardiac health (36%).[187]. Participation may also have a wider role in improving health. A significant number within a long-term heart failure trial reported changes in smoking (15%), alcohol consumption (15%) and diet (38%), although there were no interventions attempting to influence such health behaviours.[188]

Within some types of trials there may be specific benefits from participation. For example, in her personal account of breast cancer, Harrison believes trial participation will provide her with the greatest chance of receiving the best treatment. She is aware that the trial would be based within a specialist oncology unit and that there is evidence indicating trial participants may achieve a better outcome.[202] Hudmon et al similarly found that the expectation of receiving increased information, medical follow-up and being part of new research were very or extremely important benefits for 80% of the colon cancer patients.[190] The expectation of receiving treatment and information from specialists, increased monitoring and reassurance were also important for the majority of heart disease trial participants.[187]

Access to the most effective treatment was also an important incentive for participation in a range of cardiovascular (88%),[189] UK out-patient (38%),[181] and breast cancer (24%)[83] trials. This was also the case for all but one of the participants (16) in an arthritis trial.[192] The majority of parents agreed to take part out of a concern for their child's health (90%) and a 'dissatisfaction with current treatment' (82%).[97] Almost a quarter hoped to 'feel better' and 'live longer' as a result of their participation in heart disease trials.[188] Nearly all (14) within a herpes trial similarly hoped to receive better care within the trial. However, such a hope within this group is surprising, the trial required some to refrain from taking their medication for a condition that has no known cure.[68]

This belief in the experimental treatment was linked to hope for participants in oncology and Phase 1 trials. Three qualitative studies identified this as the main

motivation among a range of oncology,[196] breast cancer[193] and advanced liver cancer[197] patients. Such patients often felt they had no choice: non-participation was equated with death and hence they felt they had to do everything possible to increase their chances of survival.[193, 196, 197] 70% of those taking part in a range of cancer trials believed that they would at least gain psychologically.[191] For some, continuing medical treatment enabled them to postpone or deny that their condition was terminal.[195, 197]

The hope of obtaining the 'new' or 'experimental' treatment was also cited by many willing hypothetically to participate as their main motivation.[143, 145, 148, 179, 183] This applied to parents (44%),[148] a lay population (12.7%),[179] an African-American population (28%),[143] and gay and bisexual men asked to participate in HIV vaccine trials.[145, 183] Macqueen observed that many (37%) who were willing to participate in an HIV vaccine trial saw the vaccine itself as a possible way of reducing their personal risk.[183] Similarly, 72% of UK oncology patients welcomed the 'greater chance of receiving *new* treatments', although many (27%) also indicated that the least appealing aspect of participation was the 'chance of obtaining *experimental* treatments'.[150]

The enthusiasm and hopes of family and friends were often the driving force behind participation. Within a range of phase I,[191, 195, 196, 201] oncology[197] and cardiovascular trials,[189] respondents received pressure from their families to take part. The opinion of family and friends was a powerful motivation for all the participants (10) in a Phase I oncology trial. For example, three women who had no interest in participating did so because they were urged by their husbands "to grab their last chance"(p.460).[195] Approval of the trial by the patient's partner was a significant predictor of consent, with 97% of patients whose partners approved participating in a cardiovascular trial and 96% declining when partners objected.[189] Similarly, for a quarter of those who decided not to participate in a UK out-patient trial, their relatives were opposed to their participation.[181] Partners often assumed shared responsibility for finding treatment, sometimes in a more forceful manner than the patients themselves.[197]

Such beliefs highlight the vulnerability of some groups and the risks they are willing to take if there is a chance of survival.[196] Expectations of benefiting personally from participation are unrealistic for many of these trials and indicates poor communication about the trial. For example, many women (35%) believed they had received better care within a gynaecological trial that involved keyhole surgery performed under a general anaesthetic. However, this procedure was purely for research purposes and Lynoe et al speculate that these patients may have mistakenly assumed that this was a beneficial procedure only available within the trial.[105]

The low refusal rate within many trials, often with highly toxic treatment regimens, may be a further indication of participants' unrealistic expectations. Zwitter and Tobias found that overall only 5% of patients refused to participate in lung cancer trials due to side effects. This was consistent, even within chemotherapy trials, where higher levels of side-effects would be expected.[79] Similarly, the refusal rate was very low (6%) within the paediatric trial for acute respiratory failure. Snowdon et al found that parents did not believe there was uncertainty about the 'new' treatment and few were concerned about the possible risks. As their child's condition deteriorated, most parents believed they had nothing to loose and that the chance of a new treatment was a powerful incentive.[173]

Edwards et al in a recent (1998) systematic review also concluded that gaining personally from participation was the main motivation.[72] They suggest that such expectations, especially within trials where participants will not gain, should be explored in more detail.[72]

Satisfaction with participation

Satisfaction was high within heart disease trials, despite the fact that these patients had often taken part in these trials for several years[187] and up to four years in some cases.[188] Almost all (97%) within a long-term heart failure trial were satisfied, would repeat the experience (87%) and would recommend participation to a friend (96%).[188]. Similarly, Bevan et al[181] found that just over

half (54%) of the UK out-patients believed that there was no aspect of the trial or participation with which they were unhappy.[181]

Within a Phase 1 gene therapy trial,[201] almost all believed there had been no risk and 75% (12) did not think they had been affected by participation in what was a safety trial. Their expectations about the therapy were slightly higher after the trial, although overall they remained realistic about how much personally they would benefit. Follow-up interviews revealed that none believed that the trial had contributed to an improvement or deterioration in their condition. Those who were worried about taking part remained worried after the trial.[201]

The majority of patients within two myocardial infarction (51-87%)[187] and two Phase 1 (75-100%)[190, 201] trials would participate in future trials if asked. However, for colon cancer patients this was related to the benefits of participation. Just over half (52%) were willing to participate in a placebo trial, although this dropped to 35% if the trial did not reimburse expenses.[190]

Problems with participating

Few practical problems with trial participation were reported. Participants within heart disease trials cited travelling to the clinic (10-[187] 21%),[188] time waiting at the clinic (3-10%)[187] and changes in clinic staff (4-[187] 7%).[188] Patients within oncology and HIV trials were the only groups to report significant problems with participation. The focus was often on issues that would affect them personally. For example, the risk of infection from the wards and the general disruption to their lives of participation in the gene therapy trial were more important than the wider issues of safety and ethics associated with such treatment.[201] Qualitative studies similarly found that the demands of attending the clinic caused problems for participants in a Phase 1 trial.[196]

Information was an important issue within a phase I oncology trial. Most of these participants (7) were not told what to expect or of the procedures involved in the trial and often found this distressing.[196] The end of the trial left some oncology patients with a sense of loss. Participants often entered these trials with high

expectations, even though their condition was serious. At the end of the trial they lost contact with the research staff.[196, 197] As the treatment often does not work or only works for a short time, their hope can be replaced by anger and resignation.[196] Stetz suggests that recruiting clinicians should establish patients' reasons for participation to ensure that they have realistic expectations of the trial.[197]

Patients within an HIV phase I trial often experienced anxiety seeing others attending the trial clinic at later stages of the same disease. This may have a negative psychological impact on patients, especially those who are asymptomatic.[199] When patients initially agree to participate they may not be aware of such aspects of participation, which may force them to confront issues about their condition such as their future illness trajectory and mortality.[199] Ryan suggests that the health care setting itself had a significant impact on the experience of these participants and this may extend to other clinical trials. The clinic setting is an under-researched, 'seen but unnoticed background feature' of participation.[199]

Recruitment

The experience of being asked to participate in a trial was variable. Many patients felt that they experienced pressure to participate in cardiovascular (63%),[189] cancer and vascular (58%),[194] anaesthesia (34%),[102] and HIV (15%)[198] trials. Similarly, many UK out-patient (38%)[181] and gynaecology (9%)[105] trial participants felt obliged to comply with the recruiting clinician's request. 40% of oncology patients who had agreed to take part in a range of phase I trials believed that they had no option but to participate in the trial, no other treatment had been discussed.[191]

Patient reactions to being asked to participate in a trial differ. The point in their diagnosis at which patients are asked to take part in a trial may be significant. For example, two patients give very different personal accounts of their recruitment onto breast cancer trials. Hazel Thornton experienced feelings of isolation at being asked to participate in a trial and believes that recruiting

patients who have just received a cancer diagnosis is ethically unacceptable, damaging to the doctor/patient relationship and isolates patients at a time when support is vital.[89] In contrast, after receiving her breast cancer diagnosis, Jayne Harrison actively sought trial participation based on her prior knowledge of both RCT methodology and the uncertainties surrounding breast cancer treatment. However, she was told by her consultant that he knew which was the best treatment for her and that she "mustn't let academic niceties get in the way of the best treatment".[202]

Patient expectations and preferences

Patients' expectations of the potential benefits of the standard and experimental treatments available may be central to their decision to participate or not in a trial.[152] An examination of patients' (282) willingness to participate in a breast cancer clinical trial, for example, found that many had inaccurate expectations, often based on incorrect assumptions about the effectiveness of the standard treatment. It is suggested that participants in such trials who have high expectations of treatment may be attempting to deny the life threatening aspect of their cancer, or alternatively may not have been informed of the benefits of conventional therapy.[152]

The term 'preferences' describes "the level of satisfaction or desirability that a person associates with a particular health state (e.g. chronic angina), treatment process (e.g. hemodialysis, duration of treatment or illness), or level of participation" (pp.859). A distinction must be made between patients' informed choice where they are aware of risks and benefits of treatments and uninformed preferences.[204] A central but debatable assumption is that such preferences are measurable.[205]

Preferences can influence patients' willingness to participate. This was the main reason for refusal (23) among those eligible to participate in a breast cancer trial (147)[206] and also influenced participation within three sarcoma trials.[161] All agreed to participate in a trial comparing immunotherapy with no therapy. In

contrast, fewer were willing to be randomised when amputation was one of the treatment options. Almost all of the patients who withdrew received other treatments which caused less disruption to their lives.[161] Barofsky and Sugarbaker believe that these different rates of trial participation were due to the disparity between patients' prior experiences and expectations and the actual treatments available within the trial.[161]

A number of studies have found that participants often have strong treatment preferences. Snowdon et al found that the majority of parents preferred the 'new' experimental treatment. Most did not believe that there was uncertainty about this treatment and few were concerned about the possible risks. They were aware that the 'new' treatment was being used in other countries and thus assumed that this treatment had been proven and was safe. Treatment preferences were often based on information from the recruiting clinician, who sometimes 'inadvertently promoted a preference' (p.1349) for the 'new' treatment.[173]

Characteristics of participants

Only a small proportion of eligible patients asked to participate are actually recruited into trials (see chapter 2). Thus in an attempt to improve accrual in future trials, many studies have attempted to identify demographic predictors of participation. While there appear to be some predictors of accrual, sample sizes and accrual rates for studies vary considerably.

Education and socioeconomic status were indicators of participation within some studies. High school ($p<0.01$)[142] and college ($p<0.01$)[148, 152] education were both predictors of (hypothetical) willingness to participate in cancer trials. Psychiatric[149] and multiple sclerosis ($p<0.001$)[126] patients from higher socio-economic groups were also more likely to actually participate, as were women at high risk of breast cancer who had a high school education ($p<0.001$).[207] Correspondingly, patients with lower education levels were less likely to agree to participate in US cardiovascular trials than those who had received a higher education ($p<0.02$).[189]

In contrast, lower educational achievement was related to participation in HIV ($p<0.0003$)[144] and paediatric[97] trials. Harth and Thong suggest that "vulnerable parents may be volunteering their vulnerable children for clinical research" (p.1375). Those who volunteered their children were also significantly more likely to seek medical advice at least once a month ($p<0.001$), have fewer close friends and confidants ($p<0.001$), smoke more cigarettes ($p<0.001$) and take analgesics ($p<0.001$) and tranquillisers ($p<0.01$).[97] Similarly, psychiatric patients who were the most 'medicalised' were more likely to agree to participation.[149] In a subsequent study, Harth and Thong conclude that the informed consent process functioned as a social filter, as parents who volunteered their children for research were more likely to be from an economically and emotionally disadvantaged group.[69]

Willingness to participate was also associated with age, although this evidence is confusing. People screened for cancer ($p<0.01$),[142] and women with cancer ($p<0.001$),[152] were more likely to be willing (hypothetically) to participate if they were younger. However, those who were older were more likely to agree to participate (hypothetically) in HIV ($p<0.0002$)[144] and paediatric ($p<0.01$)[148] trials.

Health beliefs have also been identified as a predictor of participation. In a US postal survey, Mettlin et al found that those willing (hypothetically) to participate were more likely to be concerned about getting cancer, and be positive about the preventative effects of dietary interventions ($p<0.01$).[142] Similarly, Rimer et al found that participants (987) in a US breast cancer trial were more likely to have had a recent breast examination and to have a higher subjective and objective ($p<0.002$) risk of developing breast cancer.[207]

The timing of recruitment can also influence participation. Women within one breast cancer trial were more likely to agree if they were approached within two months of a relative's diagnosis of cancer. Those approached later were more likely to participate if they were non-smokers.[207]

No demographic differences were found between those hypothetically willing and unwilling to participate among African-Americans who attended two

community agencies,[143] and those eligible to participate in one breast cancer[208] and two sarcoma,[161] trials. Family composition, socioeconomic group[209] race, gender, religion and marital status[189] were similarly found to have no association with willingness to participate.

Non-participants

Few studies have examined non-participation. Those that do examine why people refuse to take part in clinical trials are predominantly set within the context of how to improve the response rate for future studies.

Although there was often an expectation that design issues would be an important reason for refusal,[209] only a small number within a few studies cited a dislike of being randomised to a treatment (4%-[148] 6%),[126] experimentation (10%),[50] the research methods or trial results (1%)[210] or gave religious or ethical reasons (3%)[210] for their refusal.

Trial design was problematic for a number of those asked to participate in hypothetical HIV vaccine trials. However, the aim of these studies was to assess the acceptability of the design of such trials. They found that many were less interested in participation if the treatment assignment was not revealed for 'months or years after the study began' (19%) or if the trial involved a placebo (11%)[145] and many would attempt to uncover their treatment assignment (15%).[146] Colorectal cancer patients who 'refused' were less willing to experience short term toxicity for a possible increase in survival and wanted greater benefits from participation and a greater say in the decision making process.[186]. Similarly, a study specifically examining patients' and clinicians' views of trial design found that design issues (97%) and randomisation (39%) were the main reason for refusals among oncology clinicians. Their patients reflected this. Objection to randomisation was the main reason for refusals among breast cancer patients (58%) and screened women (56%).[49]

Logistical problems such as transportation were mentioned as reasons for non-participation in diabetes (19%)[209] and multiple sclerosis (38)[126] trials. Inconvenience was also cited for paediatric[97] and cardiovascular (10%)[210] trial

non-participation. Similarly, the number of visits to the clinic was an important factor (42%) within a diabetes trial.[209] In contrast, time was only mentioned by a few non-participants in the multiple sclerosis (4)[126] and UK out-patient (3)[181] trials.

A distrust of modern medicine (52%) and the hospital (19%) was cited by non-participants in a paediatric trial[97] and this was also a barrier amongst ethnic minority and low income groups.[141] Concerns about side effects[97] and toxicity (4%)[50] of the new drug were similarly mentioned. Cultural sensitivity was also a factor. Trial information may not be available in the patients' first language.[141] Qualitative telephone interviews revealed that some distrust was also apparent among African Americans, Hispanics, and Native Americans. Although specific cultural and religious beliefs, moral values and folk medicine were barriers, a 'mistrust of being treated like a guinea pig' and a 'mistrust of white people' was mentioned by all groups as an important reason for their unwillingness (hypothetical) to participate.[58]

The issue of mistrust, however, mainly arose amongst those who would refuse to participate in HIV vaccine trials, who often indicated that they also had an aversion to becoming a 'guinea pig'.[145]. Many were unsure if they could trust the government (58%),[146] the institutions running the trials (15%),[183] and were uncertain of the researchers' motivations (17%).[146] There were also concerns about confidentiality (23%),[146, 147] social discrimination[184] and insurability (26%).[146] Unsurprisingly, within the HIV pilot studies, many were concerned about safety issues[184] such as HIV infection being caused by the vaccine (27-37%),[145] testing HIV positive (24%), the experimental nature of the vaccine and possible side effects (23%).[183]

Concerns about safety were also prevalent among those asked hypothetically to participate in a range of trials. Apprehension about possible side effects was a common reason for refusal among UK out-patients. Many believed they were too ill (22%) and would not want to change their current treatment.[181] The majority of parents (75%) would also refuse and this group's main concern was that the

treatment was unproven (49%).[148] Corbett et al found a quarter of the UK public, medical secretaries and medical students believed that their treatment could be adversely affected by trial participation.[180]

The number of refusals varied according to the type of trial and the severity of treatment. Four parents would not enrol their critically ill child onto a trial because of the uncertainty and risk of adverse events, not wanting their child 'used as a guinea pig' and being unable to make the decision while her child was critically ill.[211] In contrast, all the parents consented to their child's participation in a similar, although non-life threatening trial.[211]

Ryan in a qualitative study identified three barriers to participation in HIV trials: confidentiality, being identified as part of a specific social group or sexual identity and to avoid 'watching sick people'.[199] 'Watching sick people' refers to the anxiety they experienced on seeing others at later disease stages attending the clinic which may have a negative psychological impact on patients. Confidentiality was also an important consideration with patients concerned that although staff were bound by rules of confidentiality, others attending the clinic were not and could disclose their HIV status outside the trial setting.[199] Taking part in an HIV trial may also lead to their identification as HIV positive and having a specific social and sexual identity. Hence 'going public' in this way may also be a barrier to participation.[199]

Recall and understanding of trial participation

Three types of studies have examined recall and understanding of trial information. The majority of studies have focussed on patient recall rather than comprehension, often failing to disclose their criteria (see below in table 5), or based on participants' own rating of their understanding of the trial (see below in table 6). Participation rates, both hypothetical and actual have also been used to indicate the effectiveness of the informed consent procedure (see below in table 7). A smaller number of studies have defined the criteria used to evaluate participants' understanding (see below in table 8) or have asked participants to describe the trial in their own terms (see below in table 9).

Table 5: No criteria used to evaluate recall

Author	*Population assessed*	*Sample size*	*Purpose of the study*	*Outcome measurements*	*Main results*
Blair et al[201]	UK participants in a phase I safety trial of gene therapy for cystic fibrosis	(16)	The psychosocial aspects of participation	Longitudinal semi-structured interview before and after completion. Additional health measurement scales	Only 2 participants 'well informed'
Jensen et al[83]	Danish women in breast cancer trials	(34)	Evaluation of informed consent	Qualitative in-depth interviews	'good recall'
Rodenhuis et al[195]	Dutch Phase I cancer trial participants	(10)	Assess both recall and understanding	Interviews	'adequately informed'
Tindall et al[198]	Participants in an Australian HIV trial	(113)	Recall	Two groups received the consent form plus summary. The second group could also discuss participation A true/false self-completion questionnaire	44% (both groups) did not understand 'all' the information
Cox and Avis[196]	UK participants in phase I and II oncology trials	(7)	The psychosocial aspects of participation	Longitudinal semi-structured interviews before and after completion	'poor' recall

A number of studies have failed to define their criteria for evaluating recall and understanding (see table 5 above). Such studies often conclude that participants 'understand', even though some do not comprehend important aspects of trial participation, while other studies have failed to examine participants' understanding of key aspects of participation. For example, Rodenhuis et al concluded that 8 of the 10 participants within a Phase I oncology trial were 'adequately informed', even though half (4) believed that participating in an experiment and 'being used like a guinea pig' was unacceptable. A further two believed they were receiving the standard treatment that had unpredictable results.[195] Rodenhuis et al classified four participants as 'vulnerable'. For two, their lack of understanding was attributed to their 'limited intelligence' (p.460), the cognitive abilities of one was believed to have been impaired by cancer and a fourth was convinced the experimental treatment would cure her, despite attempts by the recruiting clinicians to modify these expectations.[195]

Four studies similarly failed to define their assessment of patients' knowledge of the trial or the therapy. The majority of participants in a breast cancer trial were believed to have 'good' recall[83] and in contrast, Cox and Avis found that overall, participants had 'poor' recall.[196] Blair et al in a qualitative study, judged only two participants in the gene therapy trial to be 'well informed'.[201] Tindall et al found no differences in recall between participants in an Australian HIV trial receiving written consent and those who received additional verbal information.[198] However, many (44%) of these HIV drug trial participants stated that they did not understand 'all' of the information.[198]

Recall was often used as a measure of effectiveness (see table 6 below). Such studies frequently tested participants' recall of the trial using structured questionnaires, often incorporating scales,[212] multiple choice[100, 212] and true/false questions[213].

Table 6: Recall as a measure of effectiveness

Author	*Population assessed*	*Sample size*	*Purpose of the study*	*Outcome measurements*	*Main results*
Daugherty et al[191]	US oncology patients prior to participation in a range of phase I cancer trials	(27)	Recall	Structured interview schedules with additional open-ended questions	Believed they understood-93% Only 33% knew the aim of the trial
Miller et al[212]	Patients after participation in a US drug trial	(168)	Recall	Structured survey Multiple choice, likert scales	98% could recall the informed consent procedure and believed that they understood the information provided.
The DCCT Research Group[100]	US diabetes trial		Recall	14 item multiple-choice questionnaire	Mean score of 97%
Harrison et al[213]	US intravenous drug users asked to enrol onto a Phase II HIV vaccine trial	(39)	Recall	A 17 item true/false questionnaire	Median score of 16 out of 17
Olver et al[70]	Participants in a range of Australian Phase I, II and III oncology trials	(100)	Recall	Structured interviews	60% believed they understood the consent form 52% recall their treatment 4% recalled side effects
Oddens et al[214]	Participants within a Nordic (unspecified) trial	(81)	Recall	Telephone interviews	Better recall of diagnosis than trial design

Immediately after informed consent had been obtained, participants in a US diabetes trial achieved a mean score of 97% for a multiple-choice questionnaire based on the informed consent procedure. A year later this was still high (91%).[100] Knowledge was correspondingly high among HIV vaccine trial volunteers. Two key questions: the belief that the vaccine would infect them with HIV or that the vaccine would protect them from HIV infection, were used to exclude potential participants. Harrison et al report that only three patients were excluded from the trial on this basis.[213]

However, recall does not necessarily reflect understanding. Almost all (98%) of participants in a US analgesics trial could recall the informed consent procedure and believed that they understood the information provided. However, over half (52%) could not recall possible side effects and over a quarter (29%) were unable to recollect the experimental treatments.[212] The majority (93%) within a range of US Phase I cancer trials also believed that they understood all (33%) or most

(60%) of what they had been told about the trial. However, only 33% knew the aim of the trial was to determine the maximum drug dose or the toxicity. Almost half (42%) believed that the trial was to ascertain the response of their tumour to treatment and 15% could not explain its purpose.[191] Olver et al similarly found that although 60% believed they understood the consent form, only half (52%) of these oncology trial participants could remember the name of the drug they received, and only 4% could recall potential side effects.[70]

Miller et al conclude that although participants were able to recall information about the wider issues such as the purpose of the trial, specific information about the drugs and possible side-effects was poorer.[212] In contrast, Oddens et al found that participants had better recall of the disease and therapy than the design of the trial.[214]

Many studies have evaluated the effectiveness of different methods of providing informed consent by examining participation rates. These evaluation studies examine both hypothetical[84, 215, 216] and actual[111, 174, 189] trial participation (see table 7 below).

Table 7: Studies evaluating the effectiveness of informed consent by the recruitment rates achieved

Author	*Population assessed*	*Sample size*	*Purpose of the study*	*Outcome measurements*	*Main results*
Levene et al[174]	A comparison of two UK trials of premature infants	(52)	The first trial sought parental consent before or soon after delivery, the second provided parents with more time and an additional discussion	Participation rate	Early entry-71% Additional time-43% participation rate
McLean[111]	Participants within a psychiatric trial.	Informed (104) not informed (22)	Participants informed or not of random allocation to their treatment	Participation rate	All agreed to participate
Dal-Re[215]	Spanish university students	Minimal (160) detailed information (146)	Compared two hypothetical consent forms containing different levels of information	Participation rate	Willingness to participate Minimal-4% Detailed- 11%
Ubel et al[216]	US prospective jurors	(165)	Two hypothetical trials with different preliminary results.	Participation rate	Initial willingness-75% Information indicating differences in treatment outcome- 49%
DeLuca et	(US)	(172)	To identify	Structured	No differences in

al[189]	participants within 12 cardiovascular trials		sociodemographic predictors of informed consent	interviews	consent between those given verbal and written consent and those who only had verbal information
Siminoff et al[76]	US oncology patients	47 eligible patients	Half provided with information on the risks and benefits. Half received less information	Interviews	Those provided with more information were more likely to agree to participate.
Corbett et al[180]	UK lay and medical population	Public (50) Medical - secretaries (25) students (25)	Comparison of different way of providing informed consent		Written information was preferred by 91%
Kemp et al[178]	UK Lay population	(1022)	Group A- random allocation Group B- additional information	Structured survey	No apparent differences
Appelbaum et al[42]	Patients within four US trials of psychiatry	(16)	Informed consent	Interviews after consent	8 understood the concept of randomisation
White et al[84]	US study of women with breast cancer	(75)	A long consent form giving detailed information. A similar 'medium' form omitted randomisation	Preferences	Preference for the detailed consent form

Fewer (43%) parents agreed to their child's participation when they were given additional time to consider their decision. In contrast, the majority (71%) of parents within the early entry trial agreed to their child's participation.[174] Levene et al conclude that informed consent is unlikely to be 'educated consent' or 'understanding consent' where early entry is required.[174]

Information on the effectiveness of the treatments available within a trial may effect recruitment. Initially, the majority (75%) of US jurors were hypothetically willing to participate. However, when preliminary data indicated that one treatment achieved better results, this fell to 49%.[216] Similarly, only 4% of the Spanish university students who received greater information about possible side effects compared to those presented with less information (11%) were willing hypothetically to participate. This suggested that providing more information about possible side effects can lead to lower levels of hypothetical recruitment.[215] Many participants preferred to receive detailed information.[84, 180] In contrast, McLean found that all agreed to participate in an actual psychiatric trial, despite receiving different levels of information about random allocation.[111] No differences in willingness to participate were found between those given

verbal and written information and those who only received verbal information to participate in one of 12 cardiovascular trials.[189]

However, Siminoff et al concluded that providing detailed information encouraged agreement with the clinician, rather than improving patient comprehension.[76] Half of the patients (51.6%) who received information about the benefits and risks of therapy agreed with the clinician's recommendation, compared with only 34.8% of those who received less information.

Three studies have attempted to ascertain ways to improve participants' understanding of the concept of randomisation.[42, 178, 180] It has been suggested that a focus on improving patients' understanding of the scientific method may reduce confusion and the stress experienced by those involved.[42, 173]

Appelbaum et al provided trial participants with a supplementary discussion with a neutral person trained to explain trial methodology. On follow-up, half (8) understood the concept of randomisation, suggesting that trial participants can be helped to understand the ways in which research differs from standard treatment.[42] Kemp et al similarly attempted to explain the concept of randomisation to a large scale stratified sample of UK adults. They were informed that "doctors did not influence the results by choosing, the patients would be randomly allocated to Group A and Group B and the randomisation would be a matter of chance 'rather like tossing a coin'"(p.157). However they suggest that the inconsistent results (although no details are given) indicate that few understood this concept.[178]

The preferred explanation of randomisation among members of the UK public (50), medical secretaries (25) and medical students (25) was one that made no explicit attempt to explain the role of chance. The descriptions of treatment allocation that mentioned 'the tossing of a coin' and 'names pulled from a hat' were the least popular, while the public most disliked the explicit statement of the role of the clinician.[180]

Hence, explicit details of the process of randomisation may be problematic for many people and Corbett et al[180] conclude that trialists must balance the need to

provide independent and open information against the subsequent benefit to the individual. Appelbaum et al propose a simpler consent process which does not focus on the details of the trial routinely included in consent forms such as information on minor risks and procedures.[42]

A smaller number of studies have defined the criteria used to evaluate participants' understanding (see below in table 8) or have asked participants to describe the trial in their own terms (see below in table 9).

Only six studies have defined their criteria for evaluating participants' understanding of the trial (see table 8 below). These have predominantly used structured questionnaires to assess recall of the information presented to participants as part of the informed consent procedure[68, 98, 103, 217] with a smaller number using international guidelines.[101, 105] These studies appear to be attempting to examine understanding against some objective criteria, however, such criteria are not defined by these studies and are predominantly used to inform the questionnaire design. These studies still fail to unpack the meaning of trial concepts, although a number do demonstrate that patient recall does not reflect understanding.[101, 103, 105, 217]

Table 8: Defined their criteria for evaluating participants' understanding of the trial

Author	*Population assessed*	*Sample size*	*Purpose of the study*	*Outcome measurements*	*Main results*
Postlethwaite et al[217]	After recruitment onto a UK growth hormone trial.	Parents (30) Patient (14)	The recruiting clinicians checklist of information	Semi-structured interviews	80% had a 'good' or 'very good' recall
Searight and Miller[68]	Participants in two US herpes trials White, well educated and predominantly women.	(14)	Based on informed consent procedure	Declaration of Helsinki	Aware they were 'guinea pigs' Understood they had been randomly assigned
Gallet et al[103]	Participants of a French myocardial infarction trial	(77)	"understanding of the most important details of the consent form" (p.44)	A short item self-completion questionnaire	On average recalled 60% of the informed consent form
Howard et al[98]	US Beta-blocker Heart Attack Trial (BHAT)	Participants (53) Spouses (42)	The informed consent procedure	Interviews	Knew they were taking part in research-61% That they could receive the experimental treatment or a placebo-

					55%
Lynoe et al[105]	Women participating in a Swedish gynaecological trial	(43)	Declaration of Helsinki	Postal questionnaire	81% recall of consent procedure
Susman et al[101]	Participants in a cancer (20) or obesity (24) trial (US)	(44) 7-20 yrs old	US federal guidelines	Informed consent	64% believed they understood Only 15% knew of trial procedures/risks

The highest level of recall was found amongst a White, well educated and predominantly female population taking part in a herpes trial. All of these participants (14) were aware that they were taking part in research, had been randomly assigned to their treatment, that allocation was blinded, that there were risks associated with participation and could also describe why a placebo was being used.[68] Gallet et al concluded that on average, myocardial infarction patients recalled a large proportion (60%) of the information within the trial consent form.[103] However, only 40-50% could recall the aims of the trial, knew that some patients received a placebo and others received an active treatment, the concept of double-blinding and the possible side effects and 10-25% were unaware that they could withdraw from a drug trial.[103]

Patient recall varied among women (43) who had participated in a Swedish gynaecological trial. Although the majority (81%) could recall giving their consent, 16% had no recollection of this and one participant believed she had not given her consent. Similarly,16% did not know what participation involved and many (39%) were unaware that they could withdraw from the trial.[105]

Although 64% of young people participating in an oncology or obesity trial believed they 'knew the benefits to themselves of participation', less than half understood the purpose of the research, how it benefited others, alternative treatment options or their ability to withdraw from the trial, and less than 15% knew the procedures or risks involved.[101] Similarly, although Postlethwaite et al judged the majority (80%) to have a 'good' or 'very good' understanding of the trial, 36% of these young people were unable to recall or understand any details of the trial. Poor understanding among six young people was associated with unrealistic treatment expectations and having no knowledge of possible side

effects.[217] Sussman et al speculate that patients deny the risks involved because this allows them to justify the unpleasant aspects of participation.[101]

Only half (27) of the cardiac trial participants were aware of the involvement of chance in their treatment allocation. Most of this group did not know how they had been allocated (25) and two believed that their treatment allocation was based on clinical information. Overall, only a third (18) were aware that they had been randomly allocated and that this involved a 50/50 distribution between the treatments.[98] However, five participants and their families believed that they were receiving a 'special' treatment and four believed the placebo was the standard treatment.[98]

However, there are both conceptual and methodological problems with such studies examining informed consent. One of the central problems is the difficulty of determining when informed consent has actually been achieved.[85] The majority of these studies are not from the patients' perspective and are based on recall rather than understanding. Often these studies fail to examine or define how these participants, clinicians and researchers understand these trial concepts.

There is a need for studies that do more than point out the flaws in current practice. The provision of information occurs within a social context, with trust and the quality of the doctor/patient relationship important.[85] Attitudinal and psychological barriers such as trust and the impulse to disregard potential risk, mean that even strict informed consent procedures do not guarantee understanding among these groups.[97]

Only three studies asked participants to describe the trial in their own terms using qualitative research methods (see table 9 below).[42, 173, 200]

Table 9:Participants asked to describe the trial in their own terms

Author	*Population assessed*	*Sample size*	*Purpose of the study*	*Outcome measurements*	*Main results*
Snowdon et al[173]	UK study of parents who had agreed to the participation of their newborn child with	37 (21 couples)	Understanding of randomisation	In-depth interviews	Only half of the interviews (12) did one of the parents believe their allocation was based on chance. Many believed they had been

	acute respiratory failure in a clinical trial				allocated on the basis of their individual therapeutic needs. Confusion and a 'distortion of the aims of randomisation'
Appelbaum et al[42]	Patients within four US trials of treatment for psychiatric illness	(88)	Informed consent	Observed the informed consent, interviews after consent	Understanding of randomisation-25% A third believed they had been allocated on the basis of their individual therapeutic needs.
Feathersone and Donovan[200]	Participants in the ClasP prostate trial	(20)	Understanding of randomisation	In-depth, semi-structured interviews	The involvement of chance-14 Lay interpretations of the concept

Around half of the psychiatric trial participants did not understand central aspects of the trial design. For example, many did not realise that the use of a placebo meant that some patients would not receive active treatment (42%), or that the purpose of the double-blind procedure was to ensure that the clinician would not know their treatment allocation (34%).[42] Similarly, 50% of participants in two trials where treatment dosage was restricted, expected their treatment to be adjusted to meet their individual needs and few (9%) were aware that the trial would limit their treatment in some way.[42]

The terminology used by trialists was problematic for some. The word 'trial' had different meanings for parents. Many believed that the 'new' treatment was available for a 'trial period' or on a 'trial basis', rather than a trial to evaluate the treatment's effectiveness.[173] An article based on preliminary findings from this thesis showed that trial terms used by trialists had other meanings outside the confines of randomised controlled trial. Terms such as 'trial' and 'random', for example, were understood differently by participants. In lay language, the word trial meant something that is 'tried out', while 'at random' related to things being done without purpose.[200] Roberson in a study of hypothetical trial participation (see table 1) also found that respondents from minority groups in the US were familiar with the term 'experimental study' and could describe what this meant. For example 'a study to help people' and 'an experiment where people are used as guinea pigs'. However, two thirds had not heard of the term 'clinical trial'.[58]

Randomisation

Only a small number of the studies looking at either actual or hypothetical participation have examined randomisation. However, these have predominantly assessed recall using structured instruments. Randomisation was cited as a reason for refusal within only a small number of the hypothetical trials. A general dislike of randomisation (they were given a detailed description), was the main reason colorectal cancer patients refused (63%)[186] and over half (57%) of a lay UK population sample would want to choose their own treatment, an inferred rejection of the principal of randomisation.[178] Gallet et al found that 40-50% of participants in a heart disease trial recalled randomisation[103] and this was the impetus for a small number of refusals within a paediatric (4%)[148] and a multiple sclerosis (6%)[126] trial. However, no details were given as to how these studies defined this question, although they appeared to be assessing recall using a series of closed questions.

Participants within studies of informed consent often had difficulty distinguishing research from receiving treatment within a standard therapeutic setting. This implies a failure to recognise the involvement of chance in their treatment allocation. Searight and Miller[68] found that almost all believed that they received better care within the herpes trial, although only two had a clear understanding of the difference between personal care and research procedures. Howard et al[98] also found that participants and their families believed that they were receiving a special treatment, with many believing that the trial was a therapeutic rather than experimental program. Similarly, even among 'well informed' patients within a Phase I cancer trial, Rodenhuis et al identified a clash between recall and interpretation of the treatment objectives.[195] However, only Searight and Miller[68] examined randomisation. They found that the majority of a young, well educated and predominantly female sample participating in a herpes trial were found to have a 'good' understanding of randomisation, with their descriptions often taking a 'concrete' form, for example 'they roll the dice' (pp.18-19). However, no further details were given.[68] Interestingly, recruiting

clinicians may also be unaware of this distinction between RCTs and personalised care. Flanery et al found that half of a sample of medical students believed they would benefit personally from trial participation.[99]

Only Snowdon et al,[173] Appelbaum et al[42], and Feathersone and Donovan[200] have used in-depth semi-structured interviews to examine participants' understanding of randomisation. Snowdon et al in a UK study carried out qualitative interviews with thirty seven parents (21 couples) who agreed to the participation of their newborn child with acute respiratory failure in a clinical trial.[173] Appelbaum et al observed the informed consent process, conducting interviews with patients (88) immediately after this had been obtained within four US trials of treatment for psychiatric illness.[42]

Both of these studies examine vulnerable populations asked to participate in trials and hence it was important to address their understanding of treatment allocation and how this differs from personalised care. Only Feathersone and Donovan reporting preliminary findings from this research have elicited the perspectives of participants taking part in a pragmatic trial for a common condition.[200] These findings will be considered in more detail in chapter 5.

Both Snowdon et al[173] and Appelbaum et al[42] found that many trial participants did not believe chance was involved in their treatment allocation. A large proportion of the psychiatric patients (69%) had no understanding of the basis for their treatment allocation and only a quarter (22) were considered to have a complete understanding of randomisation. Appelbaum et al suggest that patients misinterpret the aims of a trial because they are unable to differentiate between research and standard care. However, they give no indication as to how they defined such understanding, only that detailed enquiry was necessary to reveal such 'distortions' (p.22) within their accounts.[42]

Snowdon et al examined randomisation in terms of whether parents believed this was actually carried out, their understanding of why it was used and through an examination of parental reactions to their child's allocation. Parents were divided into two main categories, those who did or did not believe that their treatment

allocation was based on chance. Many had no understanding of the basis for their allocation to a treatment. In only half of the interviews (12) did one of the parents believe their allocation was based on chance. This group often used terms such as 'lottery', 'tossing a coin', 'drawing a name from a hat' and 'potluck' to describe this. However, Snowdon et al found that the recognition of the involvement of chance did not mean that these parents held a coherent model of the trial or randomisation. They concluded that only two parents totally accepted the use of randomisation.[173]

The majority of the parents rationalised randomisation and the implied uncertainty in a number of ways. Randomisation was predominantly seen as a 'gateway to the desired treatment' (p.1343), with the baby often believed to be the focus of this decision. For example, three parents used the information on the limited availability of the 'new' treatment to conclude that randomisation was used to resolve the ethical problem of deciding between two treatments when a child's life is at stake. Many parents whose babies received the standard treatment focused on the idea that risks were possibly averted by the use of randomisation. Some believed that their treatment allocation had been affected 'by beneficial or almost supernatural forces' (p.1347) or predestination.[173]

Snowdon et al and Appelbaum et al conclude that trial participants may systematically misinterpret the underlying scientific methodology and hence participate in the trial because of their belief in personalised care.[42, 173] A third of the psychiatric patients[42] and many parents[173] believed they had been allocated on the basis of their individual therapeutic needs. Appelbaum et al referred to this denial of random allocation as the 'therapeutic misconception' (p.20) and they suggest that patients filled such 'vacuums of knowledge' by constructing 'elaborate but entirely fictional' (p.21) accounts of their treatment assignment.[42]

Snowdon et al and Appelbaum et al both suggest that although participants' descriptions of the trial seemed correct, further scrutiny often revealed 'distortions' of the aims of randomisation. Snowdon et al additionally concluded that most parents were 'confused' (p.1348) about randomisation and the

methodology of the trial.[173] A recent systematic review of informed consent similarly suggested that "patients do not always grasp what information is disclosed to them" (p.44), resulting in "defects in reasoning" (p.44).[67] This was not the finding of the preliminary analysis of data from this thesis,[200] and this will be persued further in chapter 5.

Conclusion

The majority of studies examining trial participation are problematic in that they have tended to reflect the perspective of trialists with the aim often to improve accrual and by their focus on informed consent as opposed to patients' views. The reliance of some studies on hypothetical vignettes is also problematic and possibly misleading, because the perspectives of considering issues hypothetically may be different from those actually undergoing treatment or participating in research.[85]

The majority of studies have employed structured, closed questions to examine the motivation for, and satisfaction with, trial participation.[218] Edwards et al in a recent (1998) systematic review also point out that the methods employed in accessing participants' motivation vary greatly between studies. Some only provide closed, forced choice questions, few allow open responses, whilst others do not outline their rationale and hence these studies may not be comparable.[72] The main criticism of such studies is that they "only give a weak clue as to what patients had understood of the questions and hence what they meant by their responses" (p.1210).[72] Snowdon et al emphasise the need to look beyond participants' recall of information and terminology to their understanding of the underlying scientific method.[173] For example, there is little detailed information on patients' understanding of key concepts such as randomisation.[218] Comparative studies of those who take part, drop out or refuse to participate in trials have been suggested but have not yet been undertaken.[180, 187, 196] Turner and Sheon acknowledge that there may be resistance to the use of these additional methodologies.[151] However, Snowdon et al,[173] Appelbaum et al,[42] and Featherstone and Donovan[200] have shown the value of using these methods to

investigate the randomised controlled trial from the participants' perspective. It is to the methods of this latter study that I now turn.

Methodology, Design and Implementation

Introduction

In the sections that follow, the RCT within which this study is set will be described, followed by a detailed explanation of the qualitative research methods used. Included within this are details of how the qualitative study was undertaken, including methods of sampling for both participants and those who decided not to take part, the data collection and analysis.

Aims and objectives of the study

The participants' perspective of clinical trials has received little attention. The existing research record has tended to focus on hypothetical questions, or participation within trials of rare conditions or (in Snowdon et al's case) parents of critically ill babies.[173] The study reported here uses qualitative research methods to elicit the perspectives of 'ordinary' middle-aged and elderly men who require elective treatment for a common condition, and have either agreed or refused to participate in a pragmatic randomised controlled trial. The objectives were to examine these men's understanding of randomisation, their recall and understanding of information about the trial, plus an exploration of their expectations and preferences.

The research strategy was exploratory in nature and concerned with re-focusing onto the patients' experience, and so in-depth interviews were most appropriate.[219] Rather than using survey methods or structured interviews which can provide only broad classifications of people's behaviour, this approach attempts to look beneath the surface of a subject in order to examine in detail what people say and explore these trial participants' own interpretation of their experience and their search for meaning.

The context: the ClasP RCT

This study involved patients eligible for recruitment to the CLasP study. CLasP, funded by two regional NHS R&D Directorates, comprises three linked pragmatic RCTs to evaluate the effectiveness and cost effectiveness of a new technology (laser therapy - ELAP) compared with standard surgery (transurethral resection of the prostate - TURP) for men with evidence of acute or chronic retention of urine who require active intervention, and laser, TURP and conservative management (monitoring without active intervention) for men with lower urinary tract symptoms related to benign prostatic disease.[220]

Lower urinary tract symptoms are commonly found in middle aged and older men and usually occur in association with benign prostatic enlargement because of hyperplasia of the prostate gland and/or benign prostatic obstruction. Patients were included according to the severity of their lower urinary tract symptoms and low flow rates. Urodynamic tests were also used to group these men according to whether they were obstructed, equivocal or unobstructed. Patients were excluded if they were diagnosed with prostate cancer, had previous prostatic surgery, a life-expectancy of less than six months, or symptoms that meant TURP or laser therapy were unsuitable.[221]

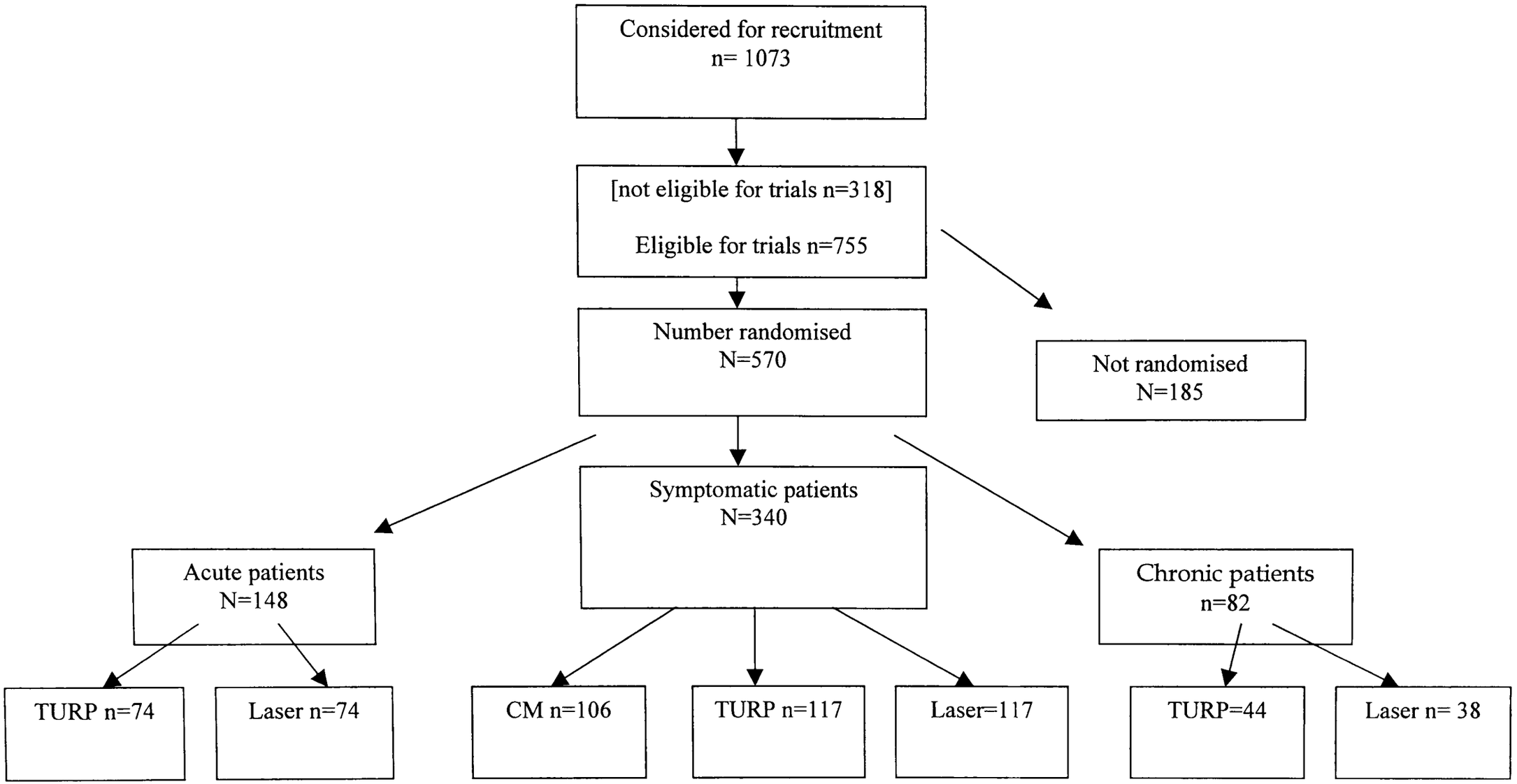
Patients randomised to laser therapy or TURP were listed for surgery within three months of randomisation. Patients randomised to conservative management were given general advice and bladder training as deemed clinically appropriate. All patients were followed up 7.5 months after randomisation.

The allocation of treatment in the CLasP study followed a protocol which consisted of a process of written informed consent, completion of questionnaires and clinical tests with eligible patients informed of their treatment allocation by clinical researchers who opened consecutive opaque envelopes. Before giving consent, patients were given an information sheet which included details about the treatments and described the study design in terms of it being called a randomised controlled trial, that it involved comparing treatments, that one of

the treatments was new (laser therapy), that there was uncertainty about which treatment was best, that allocation would be by chance and by means of the clinician opening a sealed envelope (see appendix 1). The clinicians recruiting patients were asked to explain the study in similar terms during recruitment.

Figure 1 below provides a trial profile summarising participant flow and the numbers assigned to each of the interventions. Within the group of symptomatic patients (340): 117 (34%) were randomised to laser therapy, 117 (34%) to TURP, and 106 (31%) to conservative management; 142 were recruited from Centre 1, 178 from Centre 2, and 20 from Centre 3. Acute patients (148) were randomised to TURP (74) and laser (74) and chronic patients (82) were randomised to TURP (44) and laser (38). I had access to basic information about all the men within this study and the non-participants via the clinical staff within the two recruitment centres. Before describing the characteristics of the sample and this study, the background and details of the research methods employed will be described.

Figure 1: CLasP study and symptomatic trial profile



Research methods

There is no one doctrine underlying the term 'qualitative research', rather there are a number of ideologies and methods.[222] As Denzin and Lincoln point out qualitative research does not belong to one discipline, but is employed by many differing theoretical approaches, from the constructivist perspective through to cultural studies and Marxist and feminist perspectives. It is applied within many social science disciplines, such as anthropology, cultural studies and within sociology.[223]

Qualitative research is a collection of interpretive methods, within which no single methodology is held as superior. The overall aim is to make sense of phenomena from the perspective of the individuals within the social world, emphasising the importance of the socially constructed nature of reality by examining the social world from an interpretivist, naturalistic perspective using a variety of empirical approaches such as observation, interviews, and case studies.[223] Hence the method of choice within this study was in-depth interviews within the setting of one randomised controlled trial because it allowed an exploration of the trial participants' own interpretation of their experience and their search for meaning.

Interpretivist perspectives

The foundation of the interpretivist perspective is the 18th Century German intellectual tradition of hermenuetics which focused on "trying to understand, take meaning from, or make intelligible that which is not yet understood" (p.110)[224] and the work of Hussurl who argued that the relationship between perception and objects was not passive, but that people actively developed the objects of their experience.

The interpretivist school developed particularly in reaction to the positivist perspective of the natural sciences and its influence within the social sciences which attempted to reduce social life to universal laws and the interaction of a number of variables.[225] In contrast, the interpretivists emphasised verstehen

(understanding), and the need for an interperative understanding of human action.[226] This perspective believes that for social analysis to be valid, this must relate to the meaning people give to their actions and environment which lie at the core of social interaction. 'Verstehen' provides a theory for studying social phenomena without distorting the social world of the subjects.

The interpretive approach differs from the scientific model of rational action, by focusing on how individuals make sense of the world and investigating the meanings of social phenomena.[225] Thus from the perspective of the interpretivist school, people interpret stimuli, with such interpretation continuously being revised as events take place with these in turn shaping their actions. Thus it can be seen that the same stimuli can mean differing things to different people and to the same individual at different points in time.[227] There are several sub-schools with particular approaches within the interpretivist perspective that have been influential within this study: phenomenology and symbolic interactionism.

Phenomenology

Weber, drawing upon the work of Hussurl, maintained that the individual was of more importance than 'the system'.[226] This approach sees the individual as the main unit for investigation and capable of social action. Weber defined social action as taking place when an individual gives behaviour a meaning which is related to the behaviour of others.[226] A key aspect of this approach is 'meaning' and the relationship to the type of information necessary to understand and explain social phenomena.[225] Weber believed the aim of interpretive sociology was to "interpret the actions of individuals in the social world and the ways in which individuals give meaning to social phenomena" (p.6 in Schutz).[228]

Weber introduced two principles of social science methodology: value neutrality and the use of ideal types. Value neutrality referred to the principle that social scientists must not pass off value judgements as scientific truths, because to do so would be an abuse of their scientific status. He also suggested the use of the ideal type as a method of accessing, in a more objective way, subjective meaning. Such

'models' can be developed by investigators to compare and evaluate empirical data.[225]

Schutz, in 'The Phenomenology of the social world', developed Weber's work and believed the role of sociology was to examine the "phenomenon of meaning in everyday social life" (p.44). Schutz argued that Weber failed to recognise the complexities within this or make a distinction between the way in which an interpreter modifies meaning. He believed the social world was not homogeneous, but a "complex system of perspectives" (p.8) with the 'act of attention' leading to various modifications which constitute the meaning of experiences. This creation and structure of life experiences must, he believed, be examined because this is what gives meaning to actions.[228] "Meaning is a certain way of directing one's gaze at an item of one's own experience" (p.42), thus the social world is seen as a complex system of perceptions, some shared, some unique to individuals.[228] Schutz also introduced the idea that experience can only be accessed reflectively, not when it actually occurs. The meanings of our actions are reconstructed retrospectively on the basis of memory, they are not given in an immediate way.[228]

This has important implications for interpretation, because it suggests that social scientists cannot access directly the experiences of others, but only through the interpretation of their reasons and motives. Schutz believed that the role of interpretive sociology was to "describe the processes of meaning-establishment and meaning-interpretation as these are carried out by individuals living in the social world" (p.248) in order to understand the deeper layers of understanding beyond our ordinary perception. This acknowledges the existence of multiple realities; there is no one 'truth' but lots of different and some shared truths.[228] Within the present study, this theoretical approach advocates an exploration of trial participants' own interpretation of their experience, their search for meaning and the importance of context in understanding their perspective. For example this allowed an examination of participants' understanding of randomisation

that look beyond the standard definition to explore their perspective and their process of rationalisation, after they have had time to reflect on the actual events.

Symbolic Interactionism

Symbolic interactionism is based on the work of G.H. Mead (1934), although the term was coined by Blumer[229] and is part of the interpretivist perspective. Blumer used the term symbolic interactionism to refer to the approach developed by the Chicago school of sociologists in the 20's and 30's. Symbolic interactionism stresses the importance of the human capacity to create the social world by attaching meaning to things, with such meaning arising from the process of human interaction. These meanings are also established and modified within the process of interpretation.[230]

The aim of this approach is to take into account how people being studied interpret the situation they are faced with, because this will influence their action. Blumer argued that this constructive element of human behaviour must be taken into account.[231] These meanings are the result of social interaction with others, the emphasis here being that human behaviour is constructed and can change at any point through an interperative mechanism which people use to make sense of the things they encounter. Communication is symbolic because language and other symbols are used by social actors to communicate meaning, with the process of communication also producing such symbols.[230]

This perspective places importance on the social scientist actively entering the social world of those being studied to "see the situation as it is seen by the actor, observing what the actor takes into account, observing how he (sic) interprets what is taken into account" (p.56).[229]

The main criticism of this approach is that the focus on the processes of interaction is based on a concept of social action that emphasises the symbolic aspects of social action. It therefore has limited usefulness in relation to 'phenomena of interpersonal immediacy' (p.84) and also ignores issues of power.[232] A further critique is that this descriptive approach, which privileges the

views of social actors, cannot be used to critically appraise any subsequent evaluation of the social reality they are attempting to depict.[230]

Interpretive interactionism developed from Denzin's criticism of Blumer. He believed that symbolic interactionism must become more interpretive, suggesting that it should take on board some of the developments of post-structural philosophy, such as cultural and feminist approaches in order to facilitate a closer connection between the study of meaning and interpretation. Denzin suggests that such an approach would allow the critical examination of "how interacting individuals connect their lived experiences to the cultural representations of those experiences" (p.74).[233]

Grounded Theory

These theoretical schools place little emphasis on empirical methods. With the introduction in 1967 of 'The Discovery of Grounded Theory',[234] Glaser and Strauss set out to close "the embarrassing gap between theory and empirical research" (p.vii) while also legitimating qualitative research, which at that time was not thought capable of providing satisfactory verification.[234]

Grounded theory is derived from phenomenology and is situated within the modernist, postpositivist perspective[235] and is currently the interpretive strategy most widely used by social scientists. This approach is a methodology, "a way of thinking about and conceptualising data" (p.275) and provides a specific method for theory development and verification.[235]

Glaser and Strauss stated that theory should be generated and developed, 'grounded' (p.3) through the close connection between data collection and analysis.[234] This approach involves the interpretation and understanding of the actions of those being studied from the perspectives of the participants themselves[235] and provides a systematic set of procedures in order to develop inductively derived theory about phenomena.[236] The main elements of this method are constant comparison, analysis of deviant cases and theoretical sampling.

This approach is often called the 'constant comparative' method, with verification of the main themes emerging from the research carried out through the close connection of data collection and analysis throughout the research process.[235] Grounded theory is inductive and is "discovered, developed and provisionally verified through systematic data collection and analysis of data pertaining to that phenomenon" (p.23).[236]

Theoretical sampling is the process of using the data collection as part of the generation and development of theory. The initial data collection aims to obtain a general examination of the subject area, with the objective of further data collection to develop the concepts within the analysis, for example, examining variation will add to the conceptual richness of the analysis.[235] Theoretical coding, the systematic interrogation of data to identify emerging categories or to refine existing codes, must also be carried out in conjunction with theoretical sampling and constant comparison. Such an approach allows the researcher to "conceptualize how the substantive codes may relate to each other as hypotheses to be integrated into a theory" (p.72)[237]

An important part of this approach it the 'fitness' of a theory. Deviant cases are used to test and refine theory, "a grounded theory that is faithful to the everyday realities of a substantive area is one that has been carefully induced from diverse data.....Only in this way will the theory be closely related to the daily realities (what is going on) of substantive areas, and so be highly applicable to dealing with them" (pp.238-239).[234]

The main difference between this approach and others is the focus on the development of theory, with most studies using this approach to develop substantive rather than grand theory.[235] Theory "consists of *plausible* relationships proposed among concepts and *sets of concepts*" (p.278). They are not "the formulation of some discovered aspect of a preexisting reality 'out there'" (p.279), rather they are 'fluid', taking into account process and change through the interrogation of theories to determine whether new situations fit or not.[235] In

this thesis, I employed grounded theory, and the specific methods of this research project are detailed below.

Design and methods

The aim of the research strategy was to elicit participants' experiences, therefore in-depth interviews using a semi-structured checklist of topics, were employed.[219, 227, 238, 239] This approach attempts to look beneath the surface of a subject in order to examine in detail what people say and explore trial participants' own interpretation of their experience and their search for meaning. The dominant quantitative methodologies employed within previous studies had led to a proliferation of the use of structured surveys and interview schedules to examine trial participation. Rather than using survey methods or structured interviews which rely upon assumptions about people's behaviour, this has the additional potential of revealing new areas that may not initially be anticipated.[240] One possible source of validity error is asking the wrong question,[241] and because a qualitative approach allows the continual testing of emergent theories, this can be avoided. This was important within the context of this study, for example, by allowing me to uncover participants' actual understanding of trial terminology rather than assume such comprehension.

However, the widespread use of the open-ended interview within qualitative research has been called into question.[242] As Dingwall points out, "the essential feature of interviews is that people are put on notice to talk about *something*" (p.58).[242] All experience, including private as well as public accounts are expressed through language. This in turn is evaluated for its appropriateness within a range of forms of the 'self' that are thought to be permitted within that setting.[242] Interview data are not just a series of objective facts, but active social interactions.[243] Thus interview data are social constructs developed through the participants' self-presentation and the cues the interviewer has transferred within this interaction.[242]

However, as Silverman[244] points out, although non-verbal elements of social interaction are recorded, observational data also includes a large proportion of

conversational data. Such an approach also assumes participants respond to the setting in a similar way and does not deal with the distinction between what people say and what they actually do. Thus although such an approach may reveal how people react to a specific environment, it fails to deal with how they make sense of that verbally.

The possibility of observing recruitment consultations was considered. However, at the inception of this project there was an absence of studies within the literature that provided a detailed examination of the perspectives of participants and non-participants. For example, the literature examining recall and understanding of trial information, the majority had predominantly focussed on patient recall rather than comprehension, often failing to disclose their criteria, based on participation rates, or participants' own rating of their understanding of the trial (see previously in chapter 3). Thus semi-structured interviews were thought to be a more appropriate method given the exploratory nature of this study and to facilitate the discovery of other areas not anticipated. It was believed to be important to consider these mens perspectives in detail and to examine how they reflected on the actual events of their recruitment and subsequent experience of being a trial participant or non-participant.

Sampling

Sampling in qualitative research uses non-probability methods,[219] with the sampling strategy determined by the research question and the needs of the study rather than according to external criteria. It is driven by the aim of illuminating the research question and to uncover 'multiple realities' (p.33)[245] by ensuring that the individuals included cover a range of characteristics that might have an influence on the findings and thus should include extreme or deviant cases to clarify the areas of importance.[246]

Theoretical sampling is a key aspect of grounded theory,[234] and here the aim of sampling is theoretical development rather than representativeness.[247] Hence in this study the subsequent sampling method used was stratified purposeful

sampling strategy,[245] in which individuals with particular characteristics were deliberately and systematically selected to explore emerging analytical themes.

First, data were extracted from patients' notes and this included demographic information such as age, marital status and diagnosis. If they were trial participants, information on when they were enrolled onto the trial, which procedure they were allocated to and when they received this treatment was included. For non-participants, I identified when they had been asked to participate, the reasons for refusal as recorded in the notes, which treatment (if any) they received and when they had received this treatment.

This informed the initial sampling, by allowing me to identify patients with a range of ages, treatment allocation and time since they had been approached to participate in the trial. The initial analysis led to the development of preliminary theoretical explanations, such as patients' understanding and rationalisation of their treatment allocation. This was then used to inform the next stage of data collection with the emphasis on testing and developing these initial theoretical explanations, with this in turn leading to further sampling and analysis.[247] For example, those who experienced poor outcome and participants recruited in the other clinical centre were included at later stages of sampling in order to test the preliminary findings. These men were identified with the help of the recruitment centres rather than based on trial outcome data, due to the timing of the data collection.

Thus, within this study men who chose not to participate for the range of reasons (n=11) and participants (n=22) in the CLasP study were interviewed. The experience of non-participants has rarely been explored and in this study I wanted to examine the experiences of both refusers and participants and their reasons for their decision to participate or not in the trial. The sample included men who were participating in each of the two major clinical centres, in the different arms of the trial, and at different time points.

Men who chose not to participate were the first group interviewed (11). This group was predominantly from one centre (9 from centre B) and had given a

range of reasons (according to their notes) for not participating. I did originally intend to interview more 'refusers' from centre A, however, at that stage I did not feel that further interviews with this group would assist with the development of the analysis. I thus widened my focus and interviewed twenty-two participants in the CLasP study who had been recruited within both centres.

The detailed analysis of these men's accounts took a long time to develop. These were perplexing and often contradictory accounts of participation in what is an unusual event involving a number of highly complex concepts: the randomised controlled trial. The aim of this study was to explore these men's accounts of their experiences and understanding of participation rather than to produce more general findings about the experience of trial participation.

Participants

In total, 1073 patients were considered for inclusion into the trials. However, 318 were ineligible according to the study criteria (see figure 1). 570 patients in total were entered into the three trials, with 340 to the symptomatic trial and 148 into the acute and 82 in the chronic trial. Within this study twenty two CLasP participants were interviewed: eleven from centre A and eleven from centre B. Seven were allocated to conservative management, seven to laser therapy, and eight to TURP.

The aim of the sampling was initially to talk to men from both trial centres, and included a number who had been allocated to each of the treatment arms (see table 10 within chapter 5). It was also considered important to interview men at different stages of trial participation. Thus eight men were interviewed within three months of being randomised, six within five months, and eight after they had received treatment/follow-up. Eight participants were randomised to TURP, seven to laser and seven to conservative management. At later stages of the sampling, participants who experienced poor outcome were included in order to test the preliminary findings. The majority of the participants interviewed at that time were found to have extremely successful outcome and I was concerned that these men did not represent the range of possible outcomes found more widely

within this trial. It was thought that such different outcomes may affect these mens' accounts of trial participation.

Refusers

Within the trial, 185 men were recorded as refusing to participate. Figure 1 states that eight of these were omitted in error. Of the remaining 177 eligible patients, the main reasons for non-participation as stated in their trial records were patients who did not want surgery (54), those wanting surgery (39), travel problems (19) and no reason (65). Using purposeful sampling I attempted to obtain a number of patients from each of these groups (see table 14 within chapter 6): treatment preference (5), randomisation/research (3), tests (1), travel (1) and no reason given (1).

Identification proved problematic. Originally participants were selected via the recruiting clinicians. However during some interviews it became apparent that some patients, for example, believed that they were participants even though they had been identified as non-participants. To confirm their status, I checked the trial database. Two 'non-participants' (Mr Cullum and Mr Stone) were actually participants. These patients are included within the analysis of participants within chapter 5. There were eleven confirmed non-participants.

Data collection

Contacting respondents

Gatekeepers are crucial to access the sample[223] and within this study, access to the research setting was gained via the main grant holders for the trial. I was able to sample directly from the trial database at the start of the sampling procedure and for the sampling at later stages in the project, and the registrars collecting clinical data within each centre also provided assistance. These registrars provided lists of participants from which I selected my sample. Initially this was based on the characteristics I had identified, ensuring that the sample I had selected included a number who had received each of the treatments available

within the trial. Because the treatments available within the trial were so different, patients allocated to different treatments are likely to have different experiences of trial participation. I later specifically identified participants who had a poor outcome as well as those who had improved symptoms as a result of participation. I was concerned that these men did not represent the range of possible outcomes found more widely within this trial. It was thought that such different outcomes may affect these mens' accounts of trial participation. However, because of the timing of the interviews, this was based on information provided by the trial centres, rather than trial outcome data.

There was a possibility that the gatekeepers could covertly influence my sampling by directing me towards certain types of participants. The trial staff may have found my presence threatening; I was identified as working with one of the grant holders of the trial (my supervisor), even though my primary role (student) was non-threatening. I took this into consideration in the development of my sampling strategy by specifically ensuring that the sample included a range of participants and sampled from the list of those eligible to participate.

Interview procedure

Once I obtained ethics committee approval, participants were sent an initial letter and information sheet [see appendix 2]. This described what the interview would involve, what I was interested in talking to them about, the length of the interview and assured them of confidentiality.[240] It is important that participants are provided with clear information about what the researchers want to find out about and discuss.[248]

The author (KF) carried out all of the in-depth, semi-structured interviews. Each interview began with 'breaking the ice' types of questions,[249] for example, 'Looking back, could you tell me about your prostate condition and your initial referral to the clinic?". Each interview covered the same basic issues from their initial symptoms and referral, through to recall of their recruitment onto the trial. The interviews then progressed to more focussed questions to explore their understanding and experience of the process of recruitment to the trial; feelings

about participation; experiences of treatment and outcome. The aim within the interviews was to encourage the men to relate stories about their experiences and to explore their understandings of what had happened to them. Using a topic guide (see appendix 2), the interviews were based on themes with the narrative following a sequential (chronological) order of events from their symptoms and referral to the centre with prostate problems, through to being asked to participate in the trial and ending (in some cases) with the patients' post-trial experiences.

Initially, I used the topic guide based on a format of open-ended questions that broadly covered the area I was interested in exploring. This approach allowed both the interviewer and the interviewee to deviate from this open framework at any point.[240] After the initial interviews this process became more relaxed and 'natural'[219] and during later interviews become more focused as the analysis developed.[219] New questions were introduced within some interviews, either to follow up new areas, or to test emerging theoretical insights.[240] The question order varied between interviews, following the direction of the discussion. The questions used to probe and illicit further information from the participants was also flexible, allowing the interviewer to be sensitive to the respondents' language by reflecting their wording in framing additional follow-up or probing questions.[240]

To elicit these mens' understanding of the trial and what this involved, I considered that it was important not to ask directly about their knowledge. This was significant in the light of much of the previous work within the literature at that time, some of which had asked participants if they 'understand' the information they had received about the trial or used acceptance as a proxy for understanding. Within the interviews I developed broad questions that would initiate a discussion of what happened to them that would indirectly touch on aspects of the trial and the concepts involved. Following on from that, these men's understanding could then be explored in more detail. For example, although I did not ask these men directly about their knowledge of

randomisation, this concept was discussed within the majority of the interviews. To elicit these accounts, I asked these men to tell me about how they had obtained the treatment they had received. I also reflected the terms they used within the interview to describe randomisation, such as 'the envelopes' and 'lottery'. The results of the trial were not known at the time of the interviews and both centres and informants are anonymised.

Interviews were conducted in the men's homes, at their convenience and lasted from half and hour to one and a half hours. All the respondents agreed for their interview to be audio-tape recorded, and this was the preferred method because writing notes can interfere with the flow of the interview.[240] Each interview was transcribed as fully as possible, including descriptions of non-verbal factors where appropriate. Brief field notes were also taken. These notes recorded reflections on fieldwork, the analysis, methodological issues and the research process.

Data analysis

As Hammersley and Atkinson note, analysis is not a discrete phase within the research process, rather "it begins in the pre-fieldwork phase, in the formulation and clarification of research problems, and continues through to the process of writing reports, articles and books. Formally, it starts to take shape in analytic notes and memoranda; informally it is embodied in the ethnographer's ideas and hunches" (p.205).[227]

Within this study, data collection (semi-structured interviews) and data analysis continued concurrently, according to the constant comparison methods of grounded theory (pp.101-115).[234] Qualitative data were collected and at the same time concepts and hypotheses were developed in relation to that data. Further qualitative data were then collected in relation to these emerging concepts. This approach verifies theory primarily through the relationship it has with the data, rather than through the quantity of that data.

Analysis of the data proceeded by a detailed scrutiny of the transcripts to facilitate a familiarisation with the data, in this case the interview transcripts and

listening to the tapes.[227] This 'raw' data (in this case text) was then broken down and each idea or event given a conceptual label to represent that phenonenon.[236] The first stage was to identify common themes which were coded. Coding is the initial process of data analysis and "represents the operations by which data are broken down, conceptualized, and put back together in new ways. It is the central process by which theories are built from data." (p.57)[236] The initial conceptual names were written directly onto the interview transcripts[236] and these coded segments of text were grouped, given conceptual labels[236] and included in separate word processing files.[250] These files were expanded as new transcripts were completed and were refined, focused or altered as new themes emerged. Each individual's narrative was also examined independently to establish the context and to verify the emerging themes.

Thus the initial process of coding the transcripts ensured that all the relevant data were brought together in relation to a particular category/theme. This is a form of sign posting, with data stored together under general codes with identifiers for each segment of text so that the original and subsequent locations can be traced.

Coding of the transcripts was a recurrent process. As new transcripts were coded, new categories emerged and previous transcripts were then re-examined in light of these new categories. The data were interrogated until there was an established framework of categories with which to code all the transcripts.[236] As the categories were developed and refined, so the themes become more defined.[227] The next stage was 'axial coding' (p.96), the process of developing connections and giving statements of relationships between categories and sub-categories.[236] However, this process of both open and axial coding was interchangeable and an ongoing process.[236] A number of the transcripts were also coded by my supervisor (JD), our coding was compared and discussed, leading to further development of the concepts.

The development of categories also facilitated the next step within the analysis, which was to examine the relationships between themes and categories.[236] Data

were examined for similarities and differences within themes, retaining the context of the discussion and characteristics of the individuals to aid understanding and to allow the interpretation and development of explanations.[234] Detailed descriptive accounts of groups of men were produced and these were also examined by my supervisor (JD). At this stage the data were also interrogated to check for patterns between the themes, initially by contrasting and comparison, noting where there is anything surprising or puzzling. The process of questioning such as who, what, where, how, why, is central to the development and refinement of these categories[236] and is part of the 'constant comparative method of analysis' (pp.101-106).[234]

I also looked for negative cases and examined how the data related to common-sense expectations and to what was previously known and described within others' accounts.[227] Within this study, this occurred at the sampling stage where I examined negative cases through the interviewing of non-participants and participants, selecting patients from the two main trial settings (A and B). During the analysis, I sought respondents who had or had not experienced some of the trial protocol procedures, for example the use of envelopes to reveal their allocation (see chapters 5 and 6).

An important stage in the analysis was the production of a detailed case study for each respondent (these were also checked by JD). These were detailed descriptive accounts charting each man's narrative. Typologies were also used to examine why certain strategies were adopted by some subjects[227] by tracing conditional paths to track the process of an event.[236] For example, this approach, together with the development of case studies, was used to examine the various strategies employed by each trial participant and non-participant to explain their treatment allocation. This also allowed the development of the different pathways to refusal. During this stage I often returned to the transcripts to verify categories by interrogating it for evidence to support or refute queries. This constant interplay between questioning and verification is what makes such theory 'grounded'.[236]

In light of these case studies, and the development of these strategies to explain their treatment allocation and the different pathways to refusal, all the original transcripts were once again re-examined and re-coded to check and verify the concepts as they became more defined and also to substantiate the context of the data. Sometimes I listened to the tapes themselves to check participants' emphasis on words/phrases and to re-familiarise myself with the original interviews. This led to the refinement and development of a number of themes within the analysis.

In this study, to achieve the constant comparative approach, a level of formal analysis was always achieved at least to the level of developing categories which facilitated a reflection on the fieldwork and what this was providing, before further fieldwork was carried out.[227] However the timing and timetable of the trial and its recruitment schedule led to occasional practical constraints in achieving the ideal model of close connection and interaction between the analysis and data collection at all times.

Effective data management was important. The word processing package Word for Windows was used as a way of managing the qualitative data.[251, 252] All transcripts were cross-referenced and linked to the original source,[219] facilitating the development of categories through the storage and retrieval of text during the analysis using the split screen facilities. Word for Windows allowed the sorting of transcripts, copying and pasting quotes from the original transcripts to create files with general codes such as 'treatment allocation' that emerged from the initial coding from the transcripts. These sub-category files were expanded or became focused as new categories emerged or were refined. For example, new categories such as 'the role of the clinician' and 'chance' emerged from within the general code 'treatment allocation'.

The above description of the process of analysis seems very 'clean'. However throughout this process there were periods of confusion preceding each stage of the process of analysis. This confusion is central to the development of the analysis. Through a mechanism of questioning and scepticism of categories that

emerge, ideas about relationships start as vague, tentative conjecture and speculation and develop through a process of clarification and modification. Theories are 'grounded' (p.3)[234] because they develop from the data.

Rigour

An increasing number of papers[236, 247, 253] and professional research organisations[254] provide guidelines for the assessment of the rigour of qualitative research.

There are many debates as to what criteria are appropriate. There are two main perspectives: realism, which states that there is one truth, and relativism which assumes multiple realities.[255] Some argue that the criteria developed for quantitative research should be applied, while others believe that it is inappropriate because such criteria are fundamentally incompatible with the social world and how we understand it. However, the most common assertion is that different criteria should be applied to qualitative research, although there is much debate as to what these criteria should be.[255] Silverman argues that too often qualitative researchers reject the application of validity, and argues that "it simply will not do to accept any account simply on the basis of the researcher's claims to 'an intensive personal involvement'. Immediacy and authenticity may be a good basis for certain kinds of journalism but ethnography must make different claims if we are to take it seriously" (p.153).[256] The grounded theory approach similarly states that such standards should be modified "in order to fit the realities of qualitative research, and the complexities of social phenomena" (p.250).[236]

An examination of the validity and reliability of the analysis are the main methods used to assess the rigour of qualitative research.[219] Here, validity refers to the description, the explanation and the subsequent fit between the two and the credibility of the explanation,[257] "whether the researcher sees what he or she thinks he or she sees" (p.21).[241] Hammersley defines validity within qualitative research as selective representation rather than the reproduction of reality, which is linked to judgements of plausibility, credibility and centrality.[255] An account

must be plausible when seen against our existing knowledge about the phenomenon. It should be credible, that is, that we reasonably believe the findings to be accurate, given the methods used. The centrality of the arguments must also be taken into account and the key findings within the research must be supported by greater evidence than that required for more marginal arguments.[255] Reliability is "the degree of consistency with which instances are assigned to the same category by different observers or by the same observer on different occasions" (p.67) and provides evidence of the usefulness of the research strategy employed.[255]

The use of such measures of validity is dependent upon the researcher's philosophical approach. Hence, the use of validity, reliability and generalisability within qualitative research has been criticised, with many researchers arguing that standards for judging quantitative studies are not appropriate for qualitative studies.[236]. For example, Woolcott[258] rejects validity on the grounds that there is no one 'correct' interpretation. Donmoyer[259] similarly believes that traditional notions of generalisability are inadequate because they fail to take into account research that focuses on the meaning of events for the individual. There is no objectivity; rather observations of the social world are situated within the worlds of the researcher and the researched.[223]

Theoretical validity is the main focus of the grounded theory approach, with verification of the main themes emerging from the research carried out through the close connection of data collection and analysis throughout the research process, rather than through the quantity of data collected. Theory is verified through its relationship with the data.[235] Such procedures must be explicit.[236]

Plausibility or 'member checks' can also be carried out and can take the form of asking participants to review the findings, although this is dependent upon the researcher's approach.[247, 260] However, such respondent validation has also been criticised as inappropriate,[255, 256] as participants may not be aware of the appropriateness of the findings when they are implicit within the setting.[219] Hammersley argues that "to assume that respondents can validate or even falsify

accounts in some definitive way is to forget the social character of the relationships between researcher and participants and to assume that they have privileged access to the truth. Neither of these assumptions is sustainable" (p.65).[255] An additional problem is that the research findings may be in conflict with respondents' self image.[256] In an example of using this approach, Bloor found that although this yielded some useful modifications within his research, they were not a test of those accounts and thus were not validation.[261]

Verification of the findings using secondary informants can also be used to test the accuracy and validity of the research findings. This approach must take into account the fact that some groups may have different perspectives from others.[247] Hammersley similarly points out that there is no one 'true' account of social phenomenon, but that convincing evidence can always be produced to support differing interpretations.[255]

One method often used within sociology and anthropology is 'confirmability'[260] or 'investigator triangulation',[235] where a second researcher examines the data and evaluates the categories that have emerged.[260] Within this study some transcripts were coded and detailed descriptive accounts were also checked by my supervisor (JD) and any differences were then discussed, leading to further development of the concepts. However, it is also argued that this process violates the inductive process of research that often relies on insights gained from the process of data collection. It is important that the interpretation of the principal researcher are paramount as she has the additional stock of knowledge gained from conducting the interviews.[219] Lincoln and Guba argue that such secondary researchers should be familiar with the inquiry,[260] which is the case within this study.

Triangulation can also be carried out in an attempt to safeguard validity in qualitative research, and this can be by data source, method of data collection, researcher and type of data.[262]. Data triangulation is a common method whereby a range of sources and types of data are sought.[235, 247] Within this study, although only one trial was examined, the sample included non-participants as well as

participants, participants at different stages, with 'successful' and 'unsuccessful' outcome and at different trial centres. Source triangulation was also carried out, with quotes from several respondents within the sample necessary for a category to exist.

However, the use of triangulation can prove problematic, for example it may produce contradictions within the analysis and the researcher then has to decide which account has primacy.[262] Triangulation emphasises the need to overcome the context of the data and Silverman argues that it does so to the detriment of the analysis. It is important not to ignore the context-bound nature of social interaction, and hence it may be inappropriate to develop theory based on data from different contexts.[256]

The audit trail is an important procedure for ensuring validity, and each stage within the research must be explicit so that it can be tested.[227] Hence the integrity of the research must be maintained at all stages,[247] from the sampling and data collection, to the coding and subsequent stages of the analysis and report writing. This must be a 'transparent'[263] process, such that someone unfamiliar with the research could reconstruct the procedures that took place to reach the subsequent research findings.[247, 260] This enables the reader to verify and thus have confidence in the findings, and provides the opportunity for secondary analysis of the data or replication of the study to be carried out.[236, 263]

To ensure that the research process within this study achieves such transparency, each stage of the analysis has been preserved so that all quotes can be traced back to the original transcripts and data sections are clearly labelled for retrieval and links.[263] All quotes have been tidied for public consumption, by removing anything that does not add to the meaning of a quote, such as 'um', 'er' and 'yknow'. The rationale for using the quotes presented is to illustrate the meaning of a concept and allowing the reader to judge their reaction, while balancing this with the need for all voices to be heard. Where possible within the analysis I have presented large pieces of data in the natural sequence it occurs, although this was not always practicable due to the limitations of space.

Silverman[264] points out that in the presentation of qualitative data, the reader is often left to trust the findings on the basis of a few extracts from the qualitative data set. This allows the opportunity for favoured extracts to be selected and the presentation of analysis, which although rhetorically persuasive is not theoretically convincing. To prevent this from occurring within this study, counting has been used selectively to illustrate how often phenomena or patterns occur within the data. This can be used as a way of summarising the findings to make them easier for the reader to follow,[247] qualitative research "does not imply a commitment to innumeracy" (p.10).[241]

Silverman suggests that counting techniques can provide the reader with a feeling for the data as a whole, rather than having no choice but to take the researchers' word that such findings exist. It also provides the researchers with an opportunity to test and revise their generalisations about the data.[256] An example of this approach is Silverman's analysis of clinical consultations with mothers of Down Syndrome babies. These encounters were compared to non-Down's cases by counting the number of times types of questions were asked or omitted.[264] This approach "remains qualitative since naturally occurring events on theoretical grounds are being counted" (p.112).[247] However, he cautions that counting can produce findings that are as meaningless as qualitative analysis based on selective data, "the researcher must resist the temptation to count everything" (p.165).[256] Within this study numbers have been used selectively to illustrate how often phenomena, such as the examination of their recall of trial terms, occur within the data and also to illustrate patterns, for example in the examination of the participants' beliefs about how they had been allocated to the treatment they received (see chapter 5 and 6).

The adequacy and appropriateness of the data are also crucial. Qualitative research must ensure that sufficient data are collected to achieve saturation of the categories so that any variations within them can be recognised. Within qualitative research, sampling is purposeful, continuing until there are sufficient data to confirm or refute the analysis.[219] As Mays and Pope state, qualitative

researchers must produce a "plausible and coherent explanation of the phenomenon under scrutiny" (p.110).[247] It is equally important within the presentation of the results to make a distinction between the data and the subsequent analytic interpretation of these data.[265]

This is linked to representativeness. Miles and Huberman suggest that researchers should start off with the assumption that their sample is biased and attempt to refute this statement. They suggest this could be achieved by increasing the sample, purposefully sampling for negative or extreme cases, increasing the types of cases which are poorly represented and include a random sample (not appropriate within grounded theory).[262] Evidence can also be weighted in terms of whether they are based on 'strong' or 'weak' evidence. Although their criteria for evaluating such evidence is based on participant observation methods, this can be used to indicate the strength of the conclusions reached.[262] Miles and Huberman also point out that although there is the temptation to gloss over or explain away negative cases, 'the outlier is your friend' (p.269). An examination of such cases can test and strengthen the analysis. Such negative cases can take the form of individuals, differing settings, unusual events.[262] Within this study, this occurred at the sampling stage and during the analysis.

Hammersley argues that the stark choice between relativism and realist perspectives does not have to be made, rather he suggests adopting the approach of 'subtle realism' (p.69). This approach allows an acknowledgement that there is no access to 'reality', and assumes that an account can be valid if it can accurately represent the phenomena, although this will be in the form of a 'selective representation than a reproduction of reality' (p.69).[255]

Many social scientists have provided personal statements concerning their experiences 'in the field'. Behind the research process is the 'biographically situated researcher' (p.11) who is informed by their gender, class, ethnicity and culture and from within "an interpretive community that incorporates its own historical research traditions into a distinct point of view" (p.11) and thus leading

the researcher to adopt a certain perspective of those being studied.[223] However, as Kirk and Miller[241] argue, such statements do not illuminate the research, rather they are often uncritical, providing only the 'party line' or 'rehearsed information', since it is hard not to present partial or 'laundered' biographies. It is often a criticism of qualitative research, that researchers bring their own biases into their work, but it is argued that such bias can be used as a resource. Reflexivity (see chapter 7) is an important part of this, allowing the researcher to understand their own behaviour and interpretations of their research.[266] The search for negative cases to refute or amend interpretations is a key feature of this process.[266] Miles and Huberman suggest that one way to avoid the researcher effect is to ensure that participants are aware of what the purpose of the research is, why you are there, what you are studying, how you will be collecting information and what you will do with this information.[262] The impact of these factors on the research is reported in chapter 7.

Conclusion

The empirical research carried out for this thesis, can, therefore, be described as qualitative. In-depth interviews were carried out with both participants and non-participants in a randomised controlled trial comparing surgical and conservative treatments for a common disorder in older men: lower urinary tract symptoms related to benign prostatic disease. The results are presented below within a general descriptive overview and arranged according to the themes[236] that emerged from the interview data. Non-participants were also examined in terms of their pathways to refusal. The experience of participants and non-participants are examined separately. It is to the results of the empirical research that I now turn.

The experience of trial participation

Introduction

This chapter examines participants' motivations for taking part and their perceptions of participation, including their recall of what the trial involved and how they made sense of their treatment allocation and participation. The men's symptoms, knowledge of the treatment available within the trial and outcome are also examined. A number of case studies are also described to demonstrate the dialogue that most participants engaged in to try and make sense of the trial design, set within their lay beliefs and their actual experiences of participation.

Characteristics of participants

Men (n=22) who were participating in each of the major clinical centres, in the different arms of the trial, and at different time points within the CLasP study were interviewed (see table 10 below). The sample included men aged 56-80 years old who were predominantly retired (Mr Grange, Mr Cullum, Mr Symonds were employed). Previous or present occupation and the area in which they lived were used to broadly indicate these men's social class. The majority of these men were categorised as 'working class' and four (Mr Bowler, Mr Murray, Mr Grange and Mr Bullock) as 'middle class'.

During some interviews it became apparent that some patients, for example, believed that they were participants even though they had been identified as non-participants. To confirm their status, I checked the trial database. Two 'non-participants' (Mr Cullum and Mr Stone) were actually participants and are included here.

Table 10: Participants

Name	*Age*	*Occupation*	*Arm of the trial randomised to*	*Interview time after randomisation*	*Location (Centre)*
Mr Jamison	64	Driver	CM*	3 months	B
Mr Brown	77	Builder	TURP*	3 months	B
Mr Stone	68	Café owner	Laser	3 months	B
Mr Hall	66	Civil servant	CM	3 months	B
Mr Watson	78	Retail	TURP	3 months	B
Mr Bowler	75	Accountancy	Laser	3 months	B
Mr Cooper	65	Electrician	TURP	3 months	B
Mr Taylor	73	Lorry driver	TURP	3 months	B
Mr Murray	66	Teacher	TURP	5 months	B
Mr Webster	66	Post office worker	TURP	5 months	B
Mr Grange	56	Manager	Laser	5 months	A
Mr Pierce	63	Printing firm	Laser	5 months	A
Mr Formby	72	Foreman-warehouse	CM	5 months	A
Mr Cullum	56	Salesman	CM	5 months	B
Mr Mott	66	Driving instructor	Laser	8 months	A
Mr Booth	80	Gardener	TURP	8 months	A
Mr Mills	67	Local council worker	CM	8 months	A
Mr Houghton	70	Betting shop	TURP	8 months	A
Mr Bullock	78	Engineering	Laser	8 months	A
Mr Symonds	59	Manufacturing	CM	8 months	A
Mr Flint	68	Brewery worker	Laser	8 months	A
Mr Daw	70	Washing machine repair man	CM	8 months	A

*CM = Conservative management

* TURP= Transurethral resection of the prostate (standard surgery)

Reasons for attending the urology clinic

Symptoms

The majority of these men discussed the urinary symptoms they were currently or had previously experienced that had prompted them to seek treatment (see below in table 11). The main symptoms were hesitancy, nocturia and frequency. Many described how these symptoms had impacted on their lives. Two (Mr Webster, Mr Symonds) gave only a vague indication of their condition:

> *Through the doctor. He came, I was having trouble with the water, and he said that prostate trouble [Mr Webster: allocated to TURP, preferred laser]*

> *I was having trouble with the water works you know. [Mr Symonds: allocated to CM, preferred active treatment]*

A small number of these men sought treatment initially because they had been prompted to do so by their wives:

> *It was sort of er it was the wife really, she said I should go and see someone about that like and that was it like you know [Mr Cullum: allocated to CM, no preference]*

> *Wife: I was pushing because it was a case of he wouldn't go anywhere. He was getting to be a stay-at-home because he wouldn't even go up to the shops because of the toilet 'oh I can't go there' and to do a three, four mile journey [Mr Pierce: allocated to and preferred laser]*

Table 11: Participants' reported symptoms

Name	*Frequency*	*Hesitancy*	*Nocturia*	*Affecting social life*	*Acute retention*	*Other*
Mr Jamison	✓		✓			
Mr Brown						
Mr Stone		✓		✓		
Mr Hall					✓	
Mr Watson			✓			✓
Mr Bowler			✓			
Mr Cooper						
Mr Taylor	✓	✓		✓		

Mr Murray	✓		✓			
Mr Webster						✓
Mr Grange			✓	✓		
Mr Pierce		✓		✓		✓
Mr Formby		✓	✓	✓		
Mr Cullum			✓			
Mr Mott			✓			
Mr Booth	✓					
Mr Mills						✓
Mr Houghton			✓	✓		
Mr Bullock						
Mr Symonds						✓
Mr Flint			✓	✓		
Mr Daw			✓			
TOTAL:	4 (18 %)	4 (18%)	11(50 %)	7 (32 %)	1 (5%)	5 (23% %)

A tick signifies that these men discussed this symptom within the interview.

Nocturia

Nocturia, that is, the need to urinate often during the night, was a common symptom among these participants. For a number of the men, this prompted them to seek medical advice:

> *Well no, it's the same like, more or less the same but it's annoying like to you know get out of bed, and when you go out somewhere, if you see a drop if water you've got to rush to the toilet like, you know. This is it, how I feel about it. [Mr Jamison: allocated to CM but preferred active treatment]*

> *I had no sooner got into bed but I felt I wanted to go again and I was up eight times that night and that prompted me to go to the doctors, I thought I'm fed up with this, I think I'm going to go to the doctors. [Mr Murray: allocated to and preference for TURP)*

> *I'd gone with the problem of not getting a good night sleep basically. [Mr Grange: allocated to and preferred laser]*

> *Oh yes, I would say yes because it was bad. I was getting up terrible through the night, three or four times. [Mr Mott: allocated to laser, no preference]*

Hesitancy

Hesitancy before urinating was also a problem for a number of men. This was sometimes associated with the effect their symptoms had on their social life:

> *But the thing that really made me go to the doctor about it was the fact that I used to go to the toilet and then found you couldn't pass any water and then you went away and two minutes later you were back again and you know it got a bit embarrassing going back and forwards and that was when I thought well one of these days I'm going to go and it's not going to happen and it could be permanent. [Mr Taylor: allocated to and preference for TURP]*

> *I was having so much problems in trying to pee, standing over the toilet for so long and I dreaded going into the public toilets because you could stand there forever and it just wouldn't happen so you would have to be in the privacy of somewhere so you could stand there and wait before the water actually came away. [Mr Stone: allocated to laser, preferred TURP]*

Frequency

A small number of these men mentioned frequency, that is, the need to urinate often during the day:

> *He said how many times do you go to the toilet, well fifteen times a day. Oh he said, well that's quite a bit. [Mr Murray: allocated to and preference for TURP]*

> *You know it started off going to the toilet a bit oftener that you used to [Mr Taylor: allocated to and preference for TURP]*

Retention

One participant experienced an episode of acute retention that required medical intervention:

> *I went to pass water and I couldn't pass a raindrop, I said I can't believe this, nothing. Now of course you're talking about five pints of Guinness that wants to come out and I tried and tried and I was doubled up in the end. You just don't care, they just have to take you away to the hospital and they can do what they want, you just don't care, you've gone past caring. They were very quick, no hanging about and er they did this catheter or*

whatever they call it and of course instant relief. [Mr Hall: allocated to CM, no preference]

Other symptoms

One patient discussed terminal dribbling:

> *I was getting up during the night, progressively like you know and there was other symptoms as well, will I be frank with you? well I was dribbling after I finished and I went to the doctors, I mean you hear so much about the prostate trouble now [Mr Watson: allocated to and preferred TURP]*

Affect on social life/normal daily activities

A number of men described how their symptoms affected their social life and daily activities. They often described how they had to plan journeys and experienced anxiety finding public toilets. Such experiences were often 'embarrassing' for these men:

> *And it was getting embarrassing, you're standing there and everybody was away and new people are coming in and you're still there you know and as soon as you left the toilet you were wanting to go again. [Mr Pierce: allocated to and preferred laser]*

> *Embarrassing at times, when you are at the toilet and you stand there for hours and people are in and out you know, if you are going to the pub or what have you, but I found ... [Mr Formby: allocated to CM, preferred active treatment]*

> *The only thing that really embarrassed me was trying to go to the toilet and knowing that I couldn't that I would have to stand and wait was the most embarrassing part. [Mr Stone: allocated to laser, preferred TURP]*

One participant also mentioned that his symptoms had affected his sex life:

> *But it has affected our lives sexually as well as far as the waterworks was concerned anyway, before the op. So anything was an improvement. [Mr Pierce: allocated to and preferred laser]*

Knowledge of the treatments available within the trial

Overall, these men displayed a high level of knowledge about the three treatments available within the trial: TURP, laser and conservative management. Their interpretations of what these treatments involved reflected the information contained within the trial patient information leaflets (see appendix 1).

Knowledge of TURP

Within the patient information leaflet, TURP was described as 'the most common treatment'. Almost half (10) of these patients similarly described this treatment as the *'standard operation'* (Mr Watson) or *'the conventional one'* (Mr Murray). Some of these men appeared to believe that this indicated that TURP is *'better for most people'* (Mr Murray):

> *You know you think, oh I don't know, I think I'll have the conventional one. [Mr Murray: allocated to and preference for TURP]*

> *Wife: you had a preference didn't you, there were three...*
>
> *The standard operation, yes. [Mr Watson: allocated to and preferred TURP]*

> *I think the common one must be the easiest, the one we had. [Mr Symonds: allocated to CM and preferred treatment- had TURP after the trial]*

The patient information leaflet also stated that this method involved 'cutting' and involved 'some bleeding'. This was also mentioned by a number of patients:

> *Wife: Well we looked at the things, I think it was in our mind that he'd had that many ops sort of thing he didn't really want the idea of cutting. [Mr Pierce: allocated to and preferred laser]*

> *That was always talked about of er just like taking the tissue away, that operation like. [Mr Mills: allocated to CM, preferred active treatment]*

> *Well he said to me the normal treatment, which they cut into the bladder and the penis is the most successful, [Mr Stone: allocated to laser, preferred TURP]*

The other operation seemed as if, was it a knife or something and there could be a lot of bleeding. [Mr Bowler: allocated to and preference for laser]

Knowledge of laser therapy

Within the patient information leaflet, laser therapy was described as 'a new treatment' that involved lasers. Eight of these patients similarly described laser as the new treatment:

The laser was a new system that they had been using; they had been using it for about 12 months or something. The success rate he said was pretty good, [Mr Stone: allocated to laser, preferred TURP]

I think I had already a belief in new technology. [Mr Bullock: allocated to and preferred laser]

Well gone are the days that you get there, they cut and they delve in there with instruments and that the technology they've got now is absolutely brilliant, no visible scars, no pain actually. Oh great, great, the new technology, its getting better and better. [Mr Webster: allocated to TURP, preferred laser]

The use of a laser was thought to involve *'cauterising'* (Mr Bullock) and *'burning'* (Mr Taylor):

Well it was principally that I knew that lasers in industry could be used to, very accurately and that possibly it cauterises as it cuts and I just thought that it would be the minimum amount would be removed, it sounded a better idea to me. I think I had already a belief in new technology. [Mr Bullock: allocated to and preferred laser]

I'm a bit concerned about the laser, the idea of the burning through. [Mr Murray: allocated to and preference for TURP]

I didn't to be honest like the idea of using burning or whatever they did. [Mr Taylor: allocated to and preference for TURP]

This was also thought to involve less bleeding and possibly lead to a quicker recovery:

What they said was there was very little cutting because the laser sort of closes up as it's burning so you didn't have a lot of blood. So it wasn't bad. [Mr Pierce: allocated to and preferred laser]

Because of the fact that the laser burnt it would heal quicker and it wouldn't be so much time healing, that was the main thing [...] The fact that the laser was going to heal the wound if you like almost instantly, it sounded great. [Mr Grange: allocated to and preferred laser]

Conservative management

Conservative management was identified as an acceptible treatment option by one of these men:

If they had said carry on for another six months, we'll monitor you that would have been OK. [Mr Murray: allocated to and preference for TURP]

However, this tended to be described by these men as a treatment delay, similar to the waiting list, rather than a treatment option in its own right. These patients were aware that if allocated to this treatment, they could still receive surgery after the trial.

Well it didn't bother us because I knew that eventually I would get the operation. Whether it would be six months, a year it didn't really bother us. [Mr Webster: allocated to TURP, preferred laser]

Two participants felt (rightly) that if their symptoms worsened, they would receive surgery:

Well I would have accepted that [conservative management] as well providing that if I was going to need an operation I would have had one. I think obviously I would have done and it would have just been another six months until then presumably. [Mr Flint: allocated to laser, preference for TURP]

But at the end of the day if you're really bad then I would imagine that, I don't know, they might bring the six months forward. [Mr Pierce: allocated to and preferred laser]

Perceptions of participation

Patients talked about the concepts of 'randomisation' and 'trial' a number of times during the interview. However, they often expressed their understanding in different ways.

An examination of the patient information leaflet for the trial (see appendix 1) shows that prospective participants were informed of the different treatment options available, what these treatments involved and the known effectiveness and potential side effects of these treatments based on the evidence so far. It also stated that the research project was a randomised controlled trial and that this study has been set up to find out which treatment has the best results. It went on to explain that this involved the comparison of treatments, that a sealed envelope would be opened to reveal their treatment, and (dependent on the severity of their symptoms) that they had a one in three or a one in two chance of receiving one of these treatments.

Randomisation

Based on the trial information, one could expect participants to know about randomisation in terms of six integral elements: the involvement of chance in their allocation, that envelopes were used to allocate treatments, that the treatment allocation was concealed, that treatments were being compared, that clinicians were uncertain about the most effective treatment, and that they were participating in an experiment.

One participant (Mr Mott) professed no knowledge of the trial or randomisation. He believed that the clinician would choose which treatment he would receive. He was the only one who was not able to recall or report any details about the trial or his participation.

Table 12: Participants' knowledge of randomisation

Trial participant	*Chance*	*comparison*	*envelopes*	*concealed allocation*	*experiment*	*clinical uncertainty*
Mr Murray	✓	✓	✓	✓	✓	✓
Mr Taylor	✓	✓	✓	✓		✓
Mr Pierce	✓	✓	✓	✓	✓	
Mr Houghton	✓	✓	✓	✓		✓
Mr Hall	✓	✓	✓	✓	✓	
Mr Daw	✓	✓		✓	✓	✓
Mr Cooper	✓	✓	✓	✓		
Mr Booth		✓	✓	✓		✓
Mr Flint	✓		✓	✓	✓	
Mr Cullum		✓	✓	✓		✓
Mr Bowler	✓		✓	✓		
Mr Formby	✓		✓		✓	
Mr Symonds	✓			✓	✓	
Mr Jamison	✓		✓			
Mr Grange			✓	✓		
Mr Stone		✓			✓	
Mr Brown		✓			✓	
Mr Mills	✓		✓			
Mr Watson	✓	✓				
Mr Webster	✓				✓	
Mr Bullock					✓	
Mr Mott						
TOTAL:	15 (68%)	12 (55%)	14 (64%)	13 (59%)	11 (50%)	6 (27%)

A tick signifies that the informant discussed that particular concept and that he demonstrated that he understood the concept in the way it was presented in the study information.

It can be seen in table 12 that participants were most easily able to recall that the trial involved an element of chance, with about half or more having a good recall that the study involved a comparison of treatments, an experiment and allocation by concealment, usually by envelopes. Knowledge of clinical uncertainty was at a much lower level.

No relationship was found between understanding and any of the patient characteristics. For example, the six participants who could recall five or more of these concepts had been allocated to a range of treatments, represented both trial centres and had been interviewed between three and eight months after randomisation. Age and time after randomisation appeared to have had no influence on these men's recall and understanding of trial information. The influence of social class was also examined. The four 'middle class' men had varying levels of recall and understanding of these six elements, ranging from the highest (Mr Murray) to one of the lowest (Mr Bullock).

Chance

Two-thirds (15) of the participants recalled the involvement of chance in their treatment allocation. Of these, four (Mr Houghton, Mr Formby, Mr Hall and Mr Taylor) revealed a clear knowledge of this aspect of randomisation.

> *What she said is it is a test you are going to have and we found you know, we opened one envelope and this is what you are going to have. But more than likely it could be that you were going to have one of the other tests, which I didn't mind you know. [...] I think she said that there was that kind of survey thing and depending on what envelope you picked that is what you got you know. I thought that was fair enough yes. [Mr Formby: allocated to CM, preferred active treatment]*

> *There were those three things [...] and he said oh yes you've got a swollen prostate, you'll probably have to have an operation but it's a chance you might take, which one of them you take, it comes out the hat, sort of thing you know. It's out of the hat you cannot pick. [Mr Symonds: allocated to CM and preferred active treatment]*

> *Well I'm prepared to go in and take my chance, see what they want to do. [Mr Hall: allocated to CM, no preference]*

Lay interpretation of randomisation was a common feature of such descriptions. Half of this group used terms such as '*lucky dip*' (Mr Cooper), '*pot luck*' (Mr Hall), '*toss a coin*' (Mr Webster), or '*out of the hat*' (Mr Symonds and Mr Flint) to describe the involvement of chance in their treatment allocation:

Int: So you expected it to be tailored to your needs rather than… Yes that's right, yes. Sort of toss a coin in the air and if it comes heads you get this or if it's tails you get the other. [Mr Webster: allocated to TURP, preferred laser]

But anyway I agreed to have a go at it, a bit of a lucky dip. [Mr Cooper: allocated to and preference for TURP]

It was just picked out of a hat as to which treatment you got. [Mr Flint: allocated to laser, preference for TURP]

With the use of such terms as '*out of a hat*' (Mr Jamison) and '*lottery*' (Mr Pierce) this group demonstrated a further understanding of chance. For example, it was apparent within his account that Mr Jamison was aware that this method determined access to 'treatment':

He walked away, came back with an envelope and said oh your not for surgery so I take it that they take it out of a hat and that's it, that's all I know. […] The way it looks to me is they're taking it out of their hat and if it says yes you can get it sorted out, that's how I feel about it and that's all I can tell you, you know. [Mr Jamison: allocated to CM but preferred active treatment]

However, although two participants (Mr Pierce and Mr Daw) were aware that chance was involved in their allocation, their rationalisation also incorporated a belief that fate and destiny were factors in their allocation (see also below). The use of the term '*lottery*' by Mr Pierce implies that he believes that there will be a winner among the trial participants who receives the 'best' treatment. Mr Daw also believed that there was an envelope to pick containing the 'right' treatment.

I thought it was very fair, very fair you know its pot luck what you get like. I just more or less thought well I just hope I pick the right one! You know not knowing what you are going in for sort of thing, just hope you pick the right one you know. [Mr Daw: allocated to CM, preferred active treatment]

So I went, had a consultation with one of the doctors and then he said, well you've left it a long time, then he put us through to the clinic and then, that's when I came up against the lottery.
Wife: The idea of a lottery, picking it out sort of thing, that was somebody else's choice sort of thing, even though you picked the envelope. [Mr Pierce: allocated to and preferred laser]

If you know someone who had been asked to take part, what would you say to them?
Well go for it, because you've got nothing to lose you know. At the end of the day all you've got possibly is a six month if you pick the wrong... [Mr Pierce: allocated to and preferred laser]

The comparison of treatments

Twelve participants were aware that the trial involved the comparison of treatments. For example, they were aware that participation involved testing treatments (Mr Murray and Mr Cullum) and comparing new interventions with the standard treatment (Mr Booth and Mr Pierce).

But the scheme itself was I think they wanted to compare, they wanted to do all three and then make a comparison of what the end results were. So after six months or whatever they are going to do it for, they assess it and I suppose the replies that I'm giving will help to decide what was going to go on in the future. [Mr Murray: allocated to and preference for TURP]

I was a little bit surprised that that's how they done it like you know. It was a bit er you know, but I've read different things about it, little snippets in the paper like you know about prostate things like you know. They don't know a lot about it even now I don't think, they're still sort of learning cos they're doing this study in America as well aren't they, the same sort of thing. They're linked up with Bristol, that's what they told me I think they're linked up with Bristol, Newcastle and somewhere in America as well and they are all, they're pooling all their information. I think he said America as well, yeah. [Mr Cullum: allocated to CM, no preference]

I think it [the trial] was to help other people who were going to undergo that operation and she wanted to find out what differences there were between the, I can't remember the initials now...[Int: TURPs?] TURPs was the one I had and the laser one yes. [Mr Booth: allocated to TURP, no preference]

But I think you've got to have surveys anyway to see how it compares. I mean it's not detrimental because you're still getting something done. [Mr Pierce: allocated to and preferred laser]

But evidently this, the laser treatment on the prostate, I think it's still been, that's come from America and I think they're still sort of holding sort of to see what happens with that. I think it's, with a lot of these treatments they're long term ones. [Mr Watson:

allocated to and preferred TURP]

As with chance, participants' acceptance of treatment comparison was often associated with a belief that this was helping the clinicians personally to improve their clinical skills and to help medical progress (see also below).

Concealed allocation

Thirteen participants knew that their allocation was concealed. This is associated with recalling that envelopes were used to allocate them to a treatment. Only two (Mr Symonds and Mr Daw) did not discuss concealment in the context of the use of envelopes.

> *Did you see them opening the envelopes?*
> *Yes, well you picked one and they opened the envelope. Well they opened it in front of you. [Mr Pierce: allocated to and preferred laser]*

> *I think some of the staff drew an envelope and said next time you have an appointment well you've drawn this and this is it. [Mr Flint: allocated to laser, preference for TURP]*

> *Well, I think she said that there was that kind of survey thing and depending on what envelope you picked that is what you got you know. I thought that was fair enough yes. [Mr Formby: allocated to CM, preferred active treatment]*

> *They pick the - they have three envelopes or something - and they chose the envelope where they weren't going to do nothing and the specialist said that was sort of good really because we would've suggested that we done nothing anyway like you know. So it worked out quite all right really. [Mr Cullum: allocated to CM, no preference]*

Two (Mr Hall and Mr Taylor), were also aware this involved concealment from the clinician:

> *She told me there that what they would probably do is one of two things. I would either have the laser treatment or the operation and explained that if I had the operation, such and such would happen and if I had the laser treatment what the difference would be between the two and of course at the same time explained that neither she or the consultant himself knew which I would get*

until they chose this famous envelope, one of two envelopes. [Mr Taylor: allocated to and preference for TURP]

Yes, but when I go on the [date], he's not really decided. They're going to open the envelopes, it's not like they just decide. [Mr Hall: allocated to CM, no preference]

The CLasP trial protocol and information sheets (see appendix 1) indicated that consecutive sealed envelopes were to be used for randomisation and indicated that the envelope should be opened in front of the participants. This was suggested by the trialists who assumed that seeing the envelopes being opened would help participants to believe that they had been randomly allocated to their treatment. Thirteen participants recalled hearing that consecutive opaque envelopes were involved in the trial treatment allocation and all but one was aware that this was concealed.

Er if I wanted to go on a survey then you had a choice of treatment but you didn't know which one you were going to get. I think you got two cards or three cards, a choice of three and you picked one and then they opened it in front of you and that determined which treatment you got. [Mr Pierce: allocated to and preferred laser]

I think she said there would be a choice of three envelopes you know, [Int: Yeah...] and depending on what envelope you have picked was the type of er...I think one was this type of thing that I have been on [Int: The watchful waiting?] yes [Int: conservative management?] and one was I think it was laser treatment and one was the old TURP thing you know (Int: Yes, the standard operation] that's right. So, this one came out as the waiting one you know. [Mr Formby: allocated to CM, preferred active treatment]

Yes she did, well she did explain that yes. That there was the laser treatment and there was the TURPs, the ordinary, the normal one and she mentioned another one, a therapy, tablets. I couldn't see that one being much use, not if the prostate was enlarged [...] she has them in envelopes, which operation you are going to get, or which method of treatment you are going to get. I drew the TURPs, which satisfied me, I was pretty pleased with that. [Mr Cooper: allocated to and preference for TURP]

Four participants (Mr Houghton, Mr Grange, Mr Mills and Mr Watson) had been informed that an envelope would be used to allocate them to their treatment and could recall this. However, when they did not actually see the envelope being opened, they found it difficult to believe that they had been randomised to their treatment. Their account of participation was a mixture of what actually happened to them and the information they had initially received about the trial. Any deviation from what they been told to expect *should* happen could be interpreted by them as an indication that they had not been randomised to their treatment, and that, for example, a clinician had decided:

> *Well not really, no. Because I thought when I first went on it, when she first explained it, she said you'll be given an envelope and you take your pick apparently and that never happened. [Int: Oh really, you didn't see that?] No that never happened with me, I never got offered any envelope. I was just ... that was the treatment they more or less picked out for me. [Mr Mills: allocated to CM, preferred active treatment]*

> *She mentioned envelopes to me but I think she just wandered in one day and said you've plumped for the laser treatment and that was it you know. [Mr Haughton: allocated to and preferred laser]*

> *I've just been reading it all again [re-read patient info sheet before the interview] there and I realise that [...] there was envelopes and she would draw one out and open it. But as it happened, she brought it along and said oh I've opened it, sorry, you should've seen me open it. But I didn't mind, I wasn't worried about that because I was going to ask for laser. [Mr Bowler: allocated to and preference for laser]*

In recalling the use of envelopes, Mr Grange alludes to a kind of 'predestination' and this will be taken up further below.

> *Fairly reasonable, I mean the fact that I said I'd go for the trial, I was quite happy that this was going to happen. I must say that I was fairly convinced that I was going to get a laser operation. I don't feel at all that those envelopes had anything to do with it. I never saw them drawn, that was done separately. [Mr Grange: allocated to and preferred laser]*

Clinical equipoise

The information sheet indicated that the evidence for the three treatments is equivocal and that the clinician has no treatment preference. Only six participants could recall this description of clinical equipoise or uncertainty:

> *That I don't know. I mean I've got no evidence of preference expressed by the doctors and they talked about the operation in detail and came to see me after the operation, which I thought, was very helpful. [Mr Booth: allocated to TURP, no preference]*

> *So I think it's just what you make your mind up when you hear people around you, but all the people, the doctors, the sisters whatever, they didn't say oh you should have this one, no. They were unbiased, didn't give you any impression that one was better than the other. [Mr Murray: allocated to and preference for TURP]*

> *Well ..... no because as they say, when they spoke about the two operations they explained to me then that the results should be the same all things being equal. Fair enough if that's the way They explained of course that if I had the laser treatment I would only be in for a couple of days, I would be sent home and then come back a week later. I can't say that really appealed to me, I'd rather get it all over and done with and then go home. But as I say, if I'd had to do that, then fair enough, it wouldn't have been any big problem. [Mr Taylor: allocated to and preference for TURP]*

A recollection that treatments were being compared implies an awareness of clinical uncertainty.

> *Looking at it logically, they poked around inside, discovered what was wrong and then they put it right in one of two ways, I didn't really consider the wait and see business and that's it, they've done just that. [Mr Haughton: allocated to and preferred laser]*

Participation in an experiment

Eleven participants knew they were involved in an experimental study of some sort:

> *It was ideal, no problem, no problem. They have got to have these experiments and this sort of thing and I was quite prepared you know, they've got to learn somewhere, somewhere along the line you know. [Mr Daw: allocated to CM, preferred active treatment]*

After my own doctor said would I like to go on this clinic and I said yes. I mean to say when you've got anything wrong with you, you want to get it cleared up. I didn't mind sort of being experimented on, no, no. [Mr Brown: allocated to and preferred TURP]

Well initially my doctor obviously didn't know there was a scheme running. That only cropped up after, I don't know, either the first or second visit to [hospital]. They said they were doing this trial and were there any objections and they were the people who explained the three different methods I think they were looking at. [Mr Flint: allocated to laser, preference for TURP]

It didn't matter for me, I had plenty of time on my hands so I went in for the, you know in for the after results, before, during and after. She said it would help them in their research more than anything, so why not. [Mr Webster: allocated to TURP, preferred laser]

Half of these participants used the term '*guinea pig*' (Mr Brown, Mr Symonds, Mr Hall and Mr Mills) to describe experimentation:

I don't mind being a guinea pig [laughs]. [Mr Brown: allocated to and preferred TURP]

She said, "would you mind being a sort of guinea pig you know for a test, for this clinical trial?" I said, "no, I don't mind" I says, "that's all right". [Mr Symonds: allocated to CM and preferred active treatment]

Lay understandings of trial terms

Within medical research the terms 'randomisation' and 'random allocation' have a specific meaning. This is not a haphazard method, but is a method of allocation whereby patients have an equal or known chance of being allocated to any of the trial interventions the systematic allocation of patients to treatments.[18] However, for participants, this is often given a lay interpretation as being without purpose. The dictionary similarly defines random as 'without aim or purpose or principle'.[267]

Well I suppose there's a random system, there isn't a better way really. I mean if it was just done randomly like that without anybody looking to see how certain results had gone and say oh

well we'll take that one for there, we'll do this one there. If it was done randomly like that then I suppose it's as good as any. [Mr Flint: allocated to laser, preference for TURP]

So judging by the tests and that I suppose you'd like to think I'd have this instead of that. Obviously the tests didn't show very much to bother him very much, so they just had a random. [Mr Hall: allocated to CM, no preference]

A few patients (Mr Brown Mr Bowler and Mr Haughton) were aware that there was a systematic method of allocating patients to the various treatments, although they did not see this as 'randomisation' but by some other systematic method.

Do you think they gave you enough information about the trial? Yes, like the first doctor I seen when I went out there, he said about it, different treatments and that and he said that they were like, trials and some would get one type of treatment and one the other. [Mr Brown: allocated to and preferred TURP]

I was told you just got one every so often with the laser, whether they did half a dozen in a morning or so I don't know, but I don't suppose they would just do one. [Mr Bowler: allocated to and preference for laser]

They explained that they were having this trial, that was the first I knew of it and laid out the three possibilities and said I nor her had any choice in the type. It came up on a rotation basis, so I agreed to that, fair enough. [Mr Houghton: Randomised to laser, had TURP, didn't want CM]

The use of the word 'trial' also has different meanings for trialists and patients. A trial sets out to measure and compare outcomes, that is, the events that are present or absent after participants have received an intervention allocated by randomisation.[13] However, the lay definition of a 'trial' is to test or try something out: 'a process or mode of testing qualities' or 'a trying thing or experience'.[267]

My trial didn't turn out to be one of the systems that they were, mine was two systems I would think because I had a laser and a catheter. [Mr Flint: allocated to laser, preference for TURP]

For example, Mr Murray demonstrated high recall of the trial, but assumed that he might have had to endure the 'trial' of conservative management. This

participant believes he has to 'endure' observation for six months before he can receive 'treatment', in this case the standard operation.

> *What she said was that you help us by going through this, this trial or observation and then of the end of the day they decide what they should do with you. [Mr Murray: allocated to and preference for TURP]*

Mr Bowler made a similar interpretation. He rationalised that the standard treatment could not be part of the trial because it was already in use:

> *She said there was three options, which I had already read about. One was tablets, one was the ordinary operation and one was laser. I didn't really realise that it was this scheme whereby they were a trial you know. Because I didn't think the other one is a trial (TURP), it's long standing isn't it? [Mr Bowler: allocated to and preference for laser]*

Involvement in research

Even when patients were aware that they were taking part in a trial, they often had only a partial understanding of what the trial actually involved. For example, Mr Hall and Mr Bullock assumed that this would merely entail additional '*paper work*', while Mr Pierce and Mr Formby saw the trial as a '*survey*' to assess the condition and supplement the standard treatment.

> *When they said to you would you take part, was it how you expected?*
>
> *It wasn't an inconvenience it was just some, a little bit of extra work which was of no consequence.. [...] Well it didn't conjure up any additional treatment or anything, I just saw it as some paper work to back up the normal treatment. [Mr Bullock: allocated to and preferred laser]*
>
> *What did you think of that?*
>
> *Me? Well obviously what they find can help me and maybe mean I don't have to have an operation later on and also what they find may help them with their studies I assume. [Mr Hall: allocated to CM, no preference]*
>
> *Well I imagine that if they are going to do the survey you know, like they were going to say that you are going to get the operation,*

you know that's like a continual survey of things you know. [Mr Formby: allocated to CM, preferred active treatment]

You got a lot of extra tests, but you don't know whether other people were getting it as well, so it's, the only difference was that you were having surveys to fill in which is no hardship. [Mr Pierce: allocated to and preferred laser]

In contrast, Mr Stone accepted the tests, which he assumes, are part of the experiment, despite the pain involved:

He tried to explain it to me but I think the worse experience was when he put the tubes up the penis into the bladder [...] one of the tubes slipped out. I thought well how many bloody tubes have I got in me you know. [...] He managed to get it back in again and he said fair enough, lets do it, so they did the rest of the experiment or whatever they were testing. As I say, that's another experieince I don't want to happen again. [Mr Stone: allocated to laser, preferred TURP]

Alternative, non-randomised methods of allocation

All but one (Mr Taylor) of the trial participants incorporated multiple accounts of how they might have been allocated to their treatment (although he was distrustful of this method of allocation). As previously indicated, many had a good or at least a partial recall of the major aspects of trial design and methods. However, they also believed variously that the treatments were being rationed, that treatment should have been individualised and that fate and destiny were also involved in their allocation to a treatment. Such beliefs were also associated with trust or distrust of their clinicians.

As with these men's knowledge of the trial and randomisation, age, time since randomisation and social class appeared to have no influence on their beliefs about the existence of other non-randomised methods of allocation. For example, although Mr Murray (a teacher) had the highest level of knowledge about randomisation and the trial, he also used fate and destiny and trust to make sense of the trial.

Table 13: Non-randomised methods of allocation

The 6 elements of randomisation	*Participant*	*Rationing*	*Individualised*	*Fate/ destiny*	*Trust*	*Distrust*
6	Mr Murray			✓	✓	
5	Mr Taylor					✓
5	Mr Pierce	✓	✓	✓		
5	Mr Houghton		✓		✓	✓
5	Mr Hall	✓	✓	✓		✓
5	Mr Daw			✓		
4	Mr Cooper			✓		
4	Mr Booth			✓		✓
4	Mr Flint			✓		✓
4	Mr Cullum		✓		✓	
3	Mr Bowler	✓		✓	✓	
3	Mr Formby		✓	✓	✓	
3	Mr Symonds	✓	✓			✓
2	Mr Jamison		✓		✓	✓
2	Mr Grange		✓	✓		✓
2	Mr Stone			✓	✓	✓
2	Mr Brown		✓	✓	✓	
2	Mr Mills		✓			✓
2	Mr Watson		✓		✓	
1	Mr Webster			✓		
1	Mr Bullock	✓	✓		✓	✓
0	Mr Mott					
TOTAL:		5 (23%)	12 (55%)	13 (59%)	10 (45%)	11 (50%)

Rationing

Five participants thought that the clinician might be rationing treatments using a quota system or based on patient characteristics. Almost all of this group could recall some aspects of randomisation in terms of chance (Mr Pierce, Mr Hall, Mr Bowler and Mr Symonds), that allocation was concealed (Mr Pierce, Mr Hall, Mr Bowler and Mr Symonds) and that sealed envelopes were used (Mr Pierce, Mr

Hall and Mr Bowler). Two were also aware that treatments were being compared (Mr Pierce and Mr Hall).

Four believed that they had been allocated to a treatment in order to fill a quota for that procedure. For example, Mr Bullock implies that the rationale for allocating him to a treatment was because a patient was needed to fill the quota for the laser treatment at the time he attended the clinic:

> *How about the method of treatment being decided for you?*
> *Well I think I was slightly cynical about it, I didn't really believe it. I thought that they, you know that...I really thought that they were just going to divide people up. I thought it was a bit of a con. [Mr Bullock: allocated to and preferred laser]*

These participants thought that randomisation was being used by the clinicians/the NHS as a way of rationing scarce resources. This was believed to be related to waiting list size, the limited availability of one of the treatments or cost (laser required a shorter hospital stay and conservative management effectively no additional costs at all). For example, Mr Pierce is aware of the involvement of chance, comparison of treatments, concealed allocation and the use of envelopes, which indicates some understanding of the concept of experimentation. However randomisation is also seen as a way for the recruiting clinicians to restrict access to an innovative or popular treatment:

> *Not really bearing in mind that I've had ops for the last four years so it wasn't something like...how could I put it, fair comment you know getting the different treatments. Cos that's the only way they're going to say, cos everyone would probably go for one soon as they tell you there's not much cutting you're going to go for that one aren't' you so that means they're not going to get a realistic survey. [Mr Pierce: allocated to and preferred laser]*

> *Because I thought at the time that they were wanting customers for the laser, you know that they were running short, something new, although I didn't think it was new really, I'd heard about it. [Mr Bowler: allocated to and preference for laser]*

> *Yes, but when I go on the [date], he's not really decided. They're going to open the envelopes, it's not like they just decide.*
>
> *Are you surprised they do it that way?*

Yes, yes, does that help them cut down on their operations as well? Is that their biggest time thing doing operation or not. [Mr Hall: allocated to CM, no preference]

Such beliefs were often based on these patients' experience of receiving treatment. Within this trial, laser patients were grouped together to use the laser machine in one surgical session. Hence patients receiving either laser or TURP tended only to see other patients receiving the same treatment as them on the ward and so their interpretation of what was happening was consistent:

Yes, that's the way I think, I may be wrong. Whether or not there is a chance of you getting a treatment in there I don't know. But I asked others afterwards and they all said the same, they all said the same as me. I never got any chance of getting laser. Cos I says to her, can I have the laser. [Mr Symonds: allocated to CM and preferred active treatment]

How did they decide which was the best treatment for you?
Well they done everybody in the ward you know. I suppose it was the operation. They put a thing in. [Mr Mott: allocated to laser, no preference]

Individualised treatment

Over half (12) of the participants felt that the clinician should have allocated them to a treatment based on their diagnosis and an assessment of their specific needs.

It was other doctors that I'd seen and they were very nice and you know they said like, they explained about the water test and all that and they said that I was definitely after they had examined me inside as well they said that I wanted the operation. [Mr Brown: allocated to and preferred TURP]

Do you think there's any criterion, or do you think he asked everyone?
Well no, unless the results show that I'm suitable for tests, the results from the x-rays, the blood tests and they measure the volume of water, these things, there's like a stethoscope. So I imagine he can put two and two together and decide who's most suitable for er, that's what I think... [Mr Hall: allocated to CM, no preference]

What did they tell you about the trial?
Well I wasn't concerned about the trial overall because it just seemed to be keyed in with the treatment and so the, I was told that they would decide the options. There were two options. The mechanical method of coring out the prostate and the laser and of course eventually it wasn't left to me and I received the laser treatment. [Mr Bullock: allocated to and preferred laser]

I think it would be even better if they were to tell you what they prefer, that you're going to get. Because after all with, it's going to be the first time for everybody, you don't have this thing done twice. So therefore, after all if they tell you you still don't know what it's going to be so it makes no difference. [Mr Symonds: allocated to CM and preferred active treatment]

This was often based on an assumption that this was how the various tests and examinations within the trial were utilised:

I trusted them to give me the treatment that...I thought that they may've taken into consideration age and health in deciding which ones to try, which method to try. I wasn't really bothered one way or the other, not really. [Mr Bullock: allocated to and preferred laser]

Before I had the operation, the last time I went out to [the clinic]I had to see the doctor, a gentleman a Scot's chap I think and he was very nice and he said that, cos he was the one that examined me internally as well and he said that it was enlarged and he felt that it wanted an operation so that was that. [Mr Brown: allocated to and preferred TURP]

Well what he did say was that they'll keep a check on me and then they'll play it, if things get worse then they might change their mind and decide that I do need treatment like you know. So I was quite happy with that so...[Mr Cullum: allocated to CM, no preference]

Almost all of these participants had some recall of randomisation. For example, despite being able to recall randomisation in terms of the involvement of chance, Mr Watson still believed his treatment had been individualised. Although such procedures are part of the trial, they apparently led this participant to believe that he was allocated on the basis of the test results:

They took blood samples and they said OK and they would send

for me to have an operation on the prostate [...]

Int:How was your treatment chosen from the three different options?
Yes well I think it was based on the tests that they gave me and it was one of the types. I think this was for a scan on my bladder to see if it was empty and everything and [the recruiting clinician] came back and she says to us reading the notes and everything and what had happened up to then as regards my case, in their opinion as well the middle operation was the best option they thought. [Mr Watson: allocated to and preferred TURP]

Two participants (Mr Grange and Mr Symonds) believed that certain patient characteristics were the basis for their allocation. Mr Symonds concluded that patients who were retired would be allocated to conservative management because they would have the time to complete this option:

But I thought they would probably they're only picking ones that are retired for doing that [conservative management]. I can't see them having fellas who are going to work because they wouldn't be able to do it. [Mr Symonds: allocated to CM and preferred active treatment]

Mr Grange believed that his assignment to a treatment had been based on his youth and personality type. He felt that because he was the sort of person who would '*accept new things*' he was allocated to laser, the new technology.

So how do you feel about being directed to a treatment like that?
I felt that they had looked possibly at my previous medical history and saw that the fact that I wasn't a particularly old person, I was fairly young, fairly sturdy and what have you and if you like was prepared to accept new things maybe. I think possibly they had looked at that, that was my opinion anyway. I had recently been in hospital before that, in actual fact I'd had a brain haemorrhage about twelve months previously, so they would've had plenty of medical records about me. [Mr Grange: allocated to and preferred laser]

Acceptance

Altruism and personal benefits

A small number of participants cited altruism and personal benefits of participation as a motivation for taking part in the trial. Only seven men indicated that they agreed to participate in the trial for altruistic reasons, to help clinicians to improve their clinical skills and to contribute to medical progress.

To help improve clinical skills:

> *It was just a case of well if I can help somebody else then that's the main thing at least that's the way I go through life you know. As I said to you if you'd said I would have picked you up down there rather than you walk up. If I can help anybody as I go along. [Mr Daw: allocated to CM, preferred active treatment]*

> *They did in certain things which I'm sure, which doesn't worry me because everybody's got to learn, other people have to learn and unless you've got a willing person to be able to experiment on nobody will ever learn anything anyway. I've always looked at this all my life so it doesn't make any difference. [Mr Stone: allocated to laser, preferred TURP]*

To contribute to medical progress:

> *Well not really, I don't know anything about it you see, but when it was explained to us verbally as well as in those [trial information sheets] I though well this is part of the medical progress you see. [Mr Watson: allocated to and preferred TURP]*

> *I suppose the replies that I'm giving will help to decide what was going to go on in the future. [Mr Murray: allocated to and preference for TURP]*

> *Well that don't worry me neither. If I, you know, if it's going to help research and that well, so be it, you know it might not help me but it might help somebody else later on like you know (laughs). [Mr Cullum: allocated to CM, no preference]*

A similar number (7) expected to receive some personal benefits from trial participation, including quicker treatment within the trial:

> *Yes, when I went to the hospital, I felt that this would be one of those things where you get seen and two years down the line an*

operation. When they did mention the fact that they were doing trials. I've got to admit that I immediately thought oh this could mean that I would be seen quicker and that definitely made a difference, it definitely made a difference. [Mr Grange: allocated to and preferred laser]

Again to be perfectly honest, I chose, I was quite happy to go the clinic way and at the same time at the back of my mind was, well if I go that way I might get treated quicker than if I go the other way. [Mr Taylor: allocated to and preference for TURP]

So I agreed to that, fair enough and the reason I really agreed was because I thought it would get us in quicker. She in fact said you know, if you don't do it you might wait six months [laughs] and I was in within six weeks [laughs]. [Mr Haughton: allocated to and preferred laser]

For some, this expectation was based on information they had received from the recruiting clinician:

I'd had the initial sort of interview if you like and someone came along and said would I be interested in doing a trial which involved possibly getting seen a bit quicker to start with. Which, that caught my interest to start with. So I said yes, fine. [Mr Grange: allocated to and preferred laser]

He [recruiting clinician] says, all the time you are on it he said, it accounts for any waiting time if you have got to wait for the operation you see. He said, you will probably get it done quicker, so I says fair enough, so I went on this er... programme. [Mr Mills: allocated to CM, preferred active treatment]

The patient information sheet (see appendix 1) stated that a decision not to participate would not affect their treatment. However, it was sometimes thought that taking part must have an advantage. This is linked to distrust (see below).

She say's even if you don't [volunteer], it doesn't put you right to the back of the list. Don't think that because you're volunteering you're getting help, but indirectly I think you must do. That's another point. [Mr Symonds: allocated to CM and preferred active treatment]

No, no there was no pressure, in fact she said but if you don't want to go onto it you know don't worry about it we'll just take

you in as normal. But she didn't give me any indication of how long it would be, so I don't know whether I would still have been in as quick or not, I couldn't say. I don't think I would. [Mr Cooper: allocated to and preference for TURP]

Fate/destiny

Almost two-thirds (13) of the participants held the belief that fate and destiny played a role in their treatment allocation. Such beliefs were commonly associated with acquiring their preferred treatment:

What did the envelope have for you?

It was the operation, which I thought all along I was going to get anyway. [Mr Webster: allocated to TURP, preferred laser]

Yes I think as I say I would go for the laser again and disappointment didn't come into it, because I went with the idea that it was going to be the laser and it was. [Mr Bowler: allocated to and preference for laser]

Were you surprised that they offered you an operation?

No, no I think I expected it by then. I was looking forward to the operation, I thought that, my thoughts were that at 66 if I'm getting up three times through the night now but it's not life threatening, and I do this for another five years and it gets worse and then they say well you've got to have the operation, why don't I have it now and I'll have five years of trouble free I hope. [Mr Murray: allocated to and preference for TURP]

So you didn't think they opened the envelopes?
It definitely wasn't opened in my presence. It was just brought in and said this is the one you've got and I thought to myself, I knew that before it happened. That was pre-ordained, very much so. [Mr Grange: allocated to and preferred laser]

There was also an indication that luck played a role in their allocation to their preferred treatment.

But I've been lucky, or unlucky, I've had ops but I've been lucky because other patients have commented, have I been private and I've said no... [Mr Pierce: allocated to and preferred laser]

It just came out all right for me. [Mr Formby: allocated to CM, preferred active treatment]

Well I'm not sure really, I preferred the one that I got, so I must have been lucky. I wasn't too keen on this laser idea of having the tube through the stomach into the bladder till it healed up. [Mr Cooper: allocated to and preference for TURP]

Trust

Trusting the clinician involved in the men's treatment as well as trust in medicine and the wider medical profession was evident within many accounts (10) Typically, this trust was expressed in terms of the doctor being an expert:

I don't think they can give you a choice really because you don't know do you. I mean they are the people who look at you and decide the best way, I mean there's no way an individual can decide for themselves which way to have an operation, that's the way I look at it. I mean they are the professionals I mean so what else er... [Mr Stone: allocated to laser, preferred TURP]

You know I'm quite prepared to accept the fact that these guys have to learn their profession the same as everyone else. You know it didn't inconvenience me so I was happy to go along with it. [Mr Haughton: allocated to and preferred laser]

This is associated with the altruistic desire to help others, particularly to help clinicians to improve their clinical skills, which is discussed earlier.

Trust in doctors in general was also common:

So you didn't have a preference when you went in, either TURP or the laser. The surgeon says this is what is going to happen to you and this is what he is going to do, you know. So I don't know what the laser one does you know, it just burns it out I think ha... instead of cutting it out I think. [Mr Formby: allocated to CM, preferred active treatment]

Did they talk about opening an envelope or anything?
No, no a doctor came up to see me first thing in the morning and he said well, you'll have a whatever [TURP] and about an hour or so later another doctor came up and he said unfortunately something has happened and you're going to have the laser. He said so you won't be injected but you'll be brought down and you'll be put to sleep. I said well whatever I don't care you know, I'm here, lets get on with it. So as I say from then on it just progressed. [Mr Stone: allocated to laser, preferred TURP]

For others, trusting the doctor meant that they felt the treatment allocation should be based on the findings of examinations:

> *Why don't they say we'd like you to do this, we'd like you to do that, or we'd like you to have the operation. Why don't they just tell me straight, why allocate it. [Mr Hall: allocated to CM, no preference]*

> *Well, when he examined us, you know he um, I think he thought this was the best treatment for me because when he examined us, he said, well if the prostrate was too big, it would be… I'm sure he said it would er… If it was too big, he wouldn't be able to do micro surgery or something. [Mr Mills: allocated to CM, preferred active treatment]*

However, for some, trust in the clinician meant that they would accept whatever was suggested:

> *You were told that you were allocated to laser, how did you feel about that?*
>
> *Well the decision had already been taken before I'm in the sense, if I was going to do it would I accept it and so forth really. So once a decision was taken I mean all right I'll accept it. [Mr Flint: allocated to laser, preference for TURP]*

> *When you, I look at it like this and the wife has found it the same, you want to get better so you go with it anyway, like. [Mr Brown: allocated to and preferred TURP]*

> *Well I don't know really, I thought well you know I don't suppose it worried me too much like you know, it didn't worry me too much. I thought they know what they're doing like, you know, so I sort of I'm in their hands like sort of thing, that's the attitude I took, they know more about it than what I know about it like you know. [Mr Cullum: allocated to CM, no preference]*

> *Because whatever they've asked me to I've done, you know, I'm all for it, if it's offered me I'll have it done, you know. [Mr Jamison: allocated to CM but preferred active treatment]*

This acceptance was also extended, for some, to participation in the trial itself:

> *[the recruiting clinician] opened it [the envelope], I just accepted it, it was all right. I felt confident that they were doing what the thought they should do […] I don't know if that is the case, er I*

felt that they did what was, what they thought was necessary. A friend of mine he's had some tests that I didn't get, I don't know what it is but he, and he's not on any scheme, I forget what he said it was now but it was something, whether it was an insert in measuring something or other. But, so he had something which I didn't have and he wasn't on the scheme, so I wouldn't say that I was getting more than other people. I was quite happy to go along with what they were doing, what they wanted me to do.[Mr Murray: allocated to and preference for TURP]

I just hoped that all went well with me, you know. So it's something that you just have to hope goes well. [Mr Stone: allocated to laser, preferred TURP]

It wouldn't worry me, wouldn't have worried me, I'm that sort of person, things like that don't worry me. You know I would've gone along with it, yeah. [Mr Cullum: allocated to CM, no preference]

For example, two admitted that although they would not normally agree to volunteer for anything, in this situation they felt unable to refuse:

So do you think there are any benefits to you in taking part?

Oh no not really, no. There is a fair amount of inconvenience about that sort of test. I wouldn't volunteer, it's just I don't say no. [laughs] and I'm retired as well so I've got the time. [Mr Bullock: allocated to and preferred laser]

It was, absolutely, I mean I was in the forces and you don't volunteer for anything, really. [laughs] I forgot about those rules. [Mr Bowler: allocated to and preference for laser]

Three (Mr Jamison, Mr Brown and Mr Stone) felt that they did not have the skills or knowledge to make the decision to participate or not in the trial. They were dependent upon the expertise of the recruiting clinicians:

Well he said to me the normal treatment which they cut into the bladder and the penis is the most successful, the laser one he said was more of an experimental one, how would I feel about it. I said whatever you think is best, you know. I mean I'm a layman, I don't know what goes on so I've got to leave it to them. So he said well I think we'll do it the other way we won't use the laser and it was at the last minute that they decided to use the laser. [Mr Stone: allocated to laser, preferred TURP]

I said I can remember him saying when I sat down, would I be prepared to do something or another, but I can't remember what. But I went out, up the corridor, up the stairs, I'm sure I had a photograph taken, not what for I don't know and they asked a few questions mind you know but I've been so many times that I can't remember what it's all about. [Mr Jamison: allocated to CM but preferred active treatment]

Distrust

A lack of trust in the clinicians was indicated by half (11). This was often caused by the difficulties participants had in making sense of randomisation. This often led to cynicism:

Well I think I was slightly cynical about it, I didn't really believe it. I thought that they, you know that…I really thought that they were just going to divide people up. I thought it was a bit of a con. [Mr Bullock: allocated to and preferred laser]

Now that's a thing, cos she says I was free to choose from didn't she. Now, aye, yes she gave us three, she says pick one of them. But I think along the lines afterwards, I'll be honest here, I'm dubious whether they are all the same. You know, you'll know for a fact that they're giving you the choice of picking one but you're saying to yourself, no matter which one you pick, you're not getting onto the other one. […] Yes, I think that, I don't know mind. But I think it's obviously they decide on what, what they've found out on examining you I think they decide which is going to be best for you. That's only to keep you happy I think. [Mr Symonds: allocated to CM and preferred active treatment]

When he said do I agree, or do I agree to take part in these tests, he looked at me as if, I said to myself, there's something you're not going to tell me, that I shouldn't do it or there's something funny about it, but he didn't say any more than that. So really I don't know what I've let myself in for, I know it's voluntary but it can only do good more than harm I suppose… [Mr Hall: allocated to CM, no preference]

Sister ____ gave me, she handed me two envelopes and said pick your envelope. Unless they were both the same, I don't know! [laughs] But no, as I say I think that is the best way to do it, because I can see problems otherwise, saying well so and so got a choice, I want the same sort of choice. I appreciate as I say that you have to get a fifty fifty verdict on that I would imagine. [Mr

Taylor: allocated to and preference for TURP]

For a small number (Mr Jamison, Mr Symonds, Mr Mills and Mr Bullock), a lack of trust was linked to the men's difficulty in reconciling aspects of the trial design with their own experience. For example, not seeing the envelopes was perceived by a small number to be an indication that the clinician selected their treatment:

> *Int: Right. So you think they chose that?*
>
> *They must have chose that because I wasn't given er... I know, people that have went on that course and have had the same thing and have done the ... they got to pick like, but I never got a pick of an envelope. Um, unless ... I know there was something in the form and I'm not sure, I know that I picked one of them but I don't think it was the laser thing you see, er and the questionnaire. [...] But um, I, that was more or less picked for me through er the [hospital]. wasn't really, no I wouldn't say that I was offered erm, a choice like [Mr Mills: allocated to CM, preferred active treatment]*
>
> *They still let you do the three card trick and they just carry it on because from the very first start it's written in the pamphlets they give you. That's one of the things they'll do. You've got your three choices, your TURPs, your what do you call it, this one where you're under management, but I think it would be even better if they were to tell you that they prefer, that you're going to get. Because after all with, it's going to be the first time for everybody, you don't have this thing done twice. So therefore, after all if they tell you you still don't know what it's going to be so it makes no difference... [Mr Mills: allocated to CM, preferred active treatment]*

For the majority of those who expressed distrust, this is part of their struggle to understand and can be tempered by a successful outcome. For example, in contrast to Mr Symonds above, where the failure to obtain his preference led to distrust, the fact that Mr Grange received his preferred treatment seems to have outweighed any suspicion of how this actually occurred:

> *I was convinced from the start that I was going to have a laser operation. I felt that that was what was going to be the result. I don't think the envelopes would've mattered. [Mr Grange: allocated to and preferred laser]*

Three participants (Mr Bullock, Mr Cooper and Mr Symonds) were concerned that saying no to the trial could, they believe, affect their future treatment:

> *It didn't enter my mind but I think I could've dropped out yes. I suppose at the back of your mind you are thinking, yes, but it may affect the treatment, the quality of the treatment. [Mr Bullock: allocated to and preferred laser]*

Taking part in the trial was also seen by some to be a 'trade off', a two way process whereby both parties benefited. For example, Mr Houghton and Mr Bullock believed that the clinicians had incorporated additional benefits for the patient into the trial as an inducement or 'carrot' to take part:

> *Do you think it would have been easy for you to say no?*
>
> *Yes I think I could have said no, yes I think I could have done. I would've had to have been prepared to wait and I wasn't. There's always a carrot isn't there. I mean to be honest about it they've done that deliberately so you don't say no. Well all right I understand but it's still to my benefit, so you know you go along with it. [Mr Haughton: allocated to and preferred laser]*

> *Well you know if you are part of the scheme, you're playing ball with the hospital and so they play ball with you. I wouldn't have thought of dropping out. [Mr Bullock: allocated to and preferred laser]*

Treatment preferences

All but four of the trial participants expressed a preference for one of the treatment options available as part of the trial. It is important to bear in mind that these are preferences described *after* the process of randomisation. It is not possible to know whether these preferences were present before randomisation as well as at the time of the interview.

The preferences expressed by the men suggest that over half (10) were randomised to the treatment they preferred. This was associated with fate and destiny and an expectation of individualised treatment.

> *What did you think of that?*
> *Fairly reasonable, I mean the fact that I said I'd go for the trial, I was quite happy that this was going to happen. I must say that I*

was fairly convinced that I was going to get a laser operation. I don't feel at all that those envelopes had anything to do with it. I never saw them drawn, that was done separately and I was convinced from the start that I was going to have a laser operation. I felt that that was what was going to be the result. I don't think the envelopes would've mattered. [Mr Grange: allocated to and preferred laser]

Can we just go back to the envelopes again, what would you have done if it wasn't the laser?

I think I would have asked if I could change to the laser, I think I was set on the laser. [Mr Bowler: allocated to and preference for laser]

Participants' beliefs about the trial and how they had been allocated sometimes appeared to be influenced by a preference for an alternative treatment. However, it is not known to what extent such preferences are independent of or had developed as a result of their subsequent allocation to that treatment.

Eight participants appeared to have been randomised to a treatment that was not their original or rationalised preference:

Well, I thought the standard operation. I wasn't too happy about the laser treatment because they reckoned the laser treatment would take a fortnight with a catheter in and this sort of thing which I wasn't too happy about and I thought the other one would be ideal which it was. It worked out ideal for me you know. [Mr Daw: allocated to CM, preferred active treatment]

One (Mr Webster) preferred laser but received TURP:

Brilliant, you know that's new technology. They're not going to use lasers if they're no good you know, quick, clean and efficient. So no I'd be happy with that. [Mr Webster: allocated to TURP, preferred laser]

However, this group appeared to be satisfied with their allocation, perhaps because they received 'treatment'.

Five (Mr Formby, Mr Mills, Mr Symonds, Mr Daw and Mr Jamison) preferred TURP or laser, but had been allocated to conservative management. This group had been assured that they would receive 'treatment', the standard operation

TURP, (often their treatment preference) once they had completed the trial. This was often their reason for continuing to participate:

> *You know once I put my mind to a thing I say to myself I'm going to carry it out in any case. As long as, as long as I knew at the end it was going to be put right. Cos I told her, I said once I've gone through this I hope I'm put right. She said oh aye, no problem, you'll get put right. [Mr Symonds: allocated to CM and preferred active treatment]*

> *Well it didn't bother us because I knew that eventually I would get the operation. Whether it would be six months, a year it didn't really bother us. [Mr Webster: allocated to TURP, preferred laser]*

> *Well I think what normally happens - I think I don't know how long it was, was it 9 months, 10 months or something. I think really that 9 months span or 10 months span when you finished it, I think you automatically went to the front or near the front you know. [Mr Formby: allocated to CM, preferred active treatment]*

> *Well, I said of course I want the operation, I am not coming here for fun you see. At the finish of the last time I was there, they said I notice you've ticked that you want the operation because she said, well if you hadn't ticked it, I would advise you to have it you see, which is you are probably here within a fortnight when you are gonna .. and sure enough, within a fortnight I was given a date and went to go in. [Mr Mills: allocated to CM, preferred active treatment]*

The additional tests involved in conservative management were also thought to provide benefits, for example, by screening for cancer:

> *Well just for peace of mind if you know what I mean. It would make my mind a lot easier to know that there was no, that I haven't got cancer, they're doing a thorough check. That's worth its weight in gold that having peace of mind isn't it. [Mr Webster: allocated to TURP, preferred laser]*

Or would be used to ensure that they received the most suitable treatment for them:

> *Oh I was um, well I've... it was either that or I would have just had to wait. At least I thought that something was getting done and at least they were finding something out because when I*

finally went in for the operation on the night time when I saw Mr _____, he said, well I've got some good information here, by being on the study, by monitoring different things he had to um er... He had all the information there and he said this is good information for me er... and there wasn't any problems really about the... you know, about doing the operation like. [Mr Mills: allocated to CM, preferred active treatment]

However, a few participants found their allocation to conservative management difficult to accept. Despite being able to recall the involvement of chance in their allocation, these participants also wanted and expected 'treatment'. This was often interpreted as their exclusion from treatment and this was often upsetting for these pateints.

You know at the moment, as I said like, the problem with this water trouble is you know four or five times every night and it's a bit annoying you know. I can go to the toilet, come downstairs and within a matter of minutes I've got to rush back upstairs. Well I think something ought to be done about it. [...] It was, it was because it was like, I naturally thought that they were going to do something about it but as I said I had no tablets or nothing for it, so that's all I can tell you. [Mr Jamison: allocated to CM but preferred active treatment]

I never got any chance of getting laser. Cos I says to her, can I have the laser [Mr Symonds: allocated to CM and preferred treatment]

This is associated with rationing (see above) and this failure to receive their preference led some participants to recognise the implications of trial participation and randomisation (this is discussed in more detail in chapter 7).

Outcome

Most of the men interviewed felt that their symptoms had been improved after treatment:

Well I was quite happy, because I mean there haven't been many side effects quite frankly. [Mr Watson: allocated to and preferred TURP]

Oh, they've turned out er... I think they've turned out champion, up till now anyway. [...] I haven't had any problem. [Mr Mills: allocated to CM, preferred active treatment]

No bother, no bother. You get a couple of days discomfort in hospital but that's all [Mr Haughton: allocated to and preferred laser]

Oh yes, the problem has gone away, yes. I don't have a problem at all now. It was very successful. [Mr Bullock: allocated to and preferred laser]

Some had such a good outcome, they would advise others to have it:

Oh I think I would recommend anyone to have the treatment. I know it isn't successful in every case, but it certainly has been very successful for me. [Mr Bullock: allocated to and preferred laser]

For one, the piece of mind that acute retention would not happen was an important outcome:

But the bit that worried me about going and not being able, there's none of that touch wood, but that was the thing that worried me because I'd heard of people where that had happened, where they had been rushed into hospital, that was the one thing that worried me about it but as I say that's gone completely. [Mr Taylor: allocated to and preference for TURP]

A small number, however, still experienced some symptoms following surgery. Two of these men (Mr Pierce and Mr Bowler) had received the laser treatment and this group were expected to improve more slowly:

I'd still be getting up through the night but most gentlemen that I mention that to say's Oh aye, I get up at night. Well I never used to and during the day I go about half a dozen times, only passing about 100-150ml. but, I was talking to Sister____ yesterday, she say's that's OK, it's gradually getting better, six months is usually the time when you can, evidently, say right I should be better now [Mr Bowler: allocated to and preference for laser]

Oh yes, it took a few weeks, after about 5 weeks I was beginning to despair, I thought this is not right but after seeing the doctor and him giving me this stuff to calm things down a bit, to get my balance, perfect. [Mr Cooper: allocated to and preference for

TURP]

Some patients modified their behaviour after the operation:

> *I think it's just training my bladder not to jump up if I feel and sort of just train it to put up with that little bit of pressure and it might just be accepted you know. [Mr Murray: allocated to and preference for TURP]*

> *It's helped, it's just getting confidence. You know I can go three to four hours now without going to the loo. But bear in mind prior to having any problems I used to go all day without going to the loo, you know. I might go in the morning when I went out and then late afternoon. So it's not back to that but then again it's been so long with running every two minutes. [Mr Pierce: allocated to and preferred laser]*

Complications following discharge from hospital

A number of these patients experienced short term and occasionally long term problems following treatment.

Laser

Aftercare was sometimes a problem for those who had been allocated to laser and had been discharged from hospital with a catheter bag:

> *I thought to myself this is great, but it wasn't great, I found out it wasn't great, wasn't as easy as you think. I didn't know what your experiences are with meeting different people like myself. But I found out that the problem is just started then, after you've come out of hospital, when you think your fit but you're not.*
>
> *Did it take some time for you to recover?*
>
> *It took months actually. [Mr Symonds: allocated to CM and preferred active treatment]*

> *I came home, I had to get someone to take me home and I had that catheter in me for three weeks, I didn't expect it to be in for so long. [Mr Grange: allocated to and preferred laser]*

> *Well I think that, well not from experience of course but I got the impression that the recovery was longer and of course they put a catheter in through the stomach wall, yes in here which seemed to me to be a lot more elaborate than the other method and also although they said it would take a fortnight before that was away*

I did have the bag for twice as long as they said, it was in for four or five weeks, it was quite a long time. [Mr Bullock: allocated to and preferred laser]

I did have quite a few problems, yes. I mean I ended up with a catheter for two weeks instead of the bag from the bladder. [Mr Flint: allocated to laser, preference for TURP]

Support after they had been discharged from the hospital and reassurance about their progression was sometimes sought:

Once I had had the operation I had this yearning all the time to urinate and nobody ever mentioned that at all. For the first couple of days I'd gone home I actually phoned the hospital two or three times to find out was there something wrong. Now if somebody had said to me after you have this operation you are going to have this feeling all the time I would've been quite happy. Well not happy but I would have been aware of the fact, so they didn't make me aware of that. Eventually Sister ____ after a week I phoned her and she said well possibly what's doing it it's the catheter is possibly touching something and if you tried pulling the catheter it might ease a little bit but that was after a week. Now if somebody had told me beforehand that sometimes the catheter can cause irritation and you can do this to alleviate this I would've done it. I was unaware of this and I had to find that out through frustration and through the telephone. [Mr Grange: allocated to and preferred laser]

TURP

A small number of patients who had received TURP also experienced prolonged pain and bleeding after they had been discharged from hospital:

I think if I had had, mind at the time, while, after this, when this pain was going on I thought I wish I'd never ever gone to the doctor about this. Now that it's over and now that it has settled down I can say yes, I'm glad that it's over. [Mr Murray: allocated to and preference for TURP]

These men were also unsure about what to expect following treatment and who to contact for advice if they were having problems:

For a long time, actually months every time I passed water I had pain and I was, it was getting me down, the people I was talking to, nobody's had this bother and I thought why is it that I'm

having so much pain and I phoned Sister ____ a few times, she was helpful and then she made arrangements for me to see, come back up to the hospital and I saw this Dr ____ and he didn't examine me he just told me- that was a bit annoying because if he had just said over the phone well it takes time but he let me get up to the hospital and then he said well it takes time and I thought well why bring me up and wait for me to see my turn for you to just tell me that, that's no help. Anyway, it did take time and I phoned, I spoke to Sister ___ two or three times on the phone about this and what she said was I'll see Dr____, there is a tablet, not the antibiotic, but the tablet which settles you down a bit [..]and eventually the pain did go away and since then I've been fine, I've been great. [Mr Murray: allocated to and preference for TURP]

One of these men described a more serious complication following surgery:

Well what went wrong was apparently there was a leakage from the tube into the bladder and they had to take it out and I think I must have had peritonitis. As far as I understand it, I obviously know nothing about it, I was in intensive care for 36 hours and they had to give me the electric treatment to get my heart going again and so forth. [Mr Flint: allocated to laser, preference for TURP]

Sexual function

Retrograde ejaculation was a side effect following surgery for four of these men. Although this is a known side effect of surgery for this condition, this was unexpected for a number of these men.

Two of these men did not remember being told about this side effect until after this had happened to them:

About the problem you were having [retrograde ejaculation]?

Yes and he said that I should've been told. Well they never told me, they never told me at all.[...] I went to my own doctor when it happened because when I first came out of the hospital it was all right but afterwards, well just a short while, after I went out of S_____ the last time, time before that it sort of happened all of a sudden. But I said to the wife, they never told me anything, whether it was just one of these things because at the time I went in to have the operation they were very very busy in there, they were coming in and out like a conveyor belt sort of business [Mr Brown: allocated to and preferred TURP]

> *I know I might be wrong, I probably am, cos you know they're cutting you and they just slipped to one side and cut through the wall a bit and that's you, that part of it's finished. You are not going to ejaculate any more and you'll say that's it, that's finished and you just wonder if it's because they've using, because they tell you, ___ told us that this does not, when I've been back I've mentioned this to the doctor, I've mentioned this I say, I can't understand this thing. He says were you not told, I says I was, but I didn't realise that it would happen and I says I didn't think that would happen. But, could you tell me does that happen all the time? Cos they told me it would just be normal you see and I found out that it wasn't so. That's the only thing that has made a difference. But otherwise everything is OK. [Mr Symonds: allocated to CM and preferred active treatment]*

One did recollect that he had been informed about this side effect before his operation, however, he did not feel that this had been clearly explained to him:

> *There was, if you don't mind this is going to get on the sexual side. He did say to me that once you had the laser treatment through the penis it will effect you in the sexual side so I said well how. He said well er the sperm that comes through from the testicles won't come that way any more. So I said why not, he said well, he still didn't explain it to me properly he said you can still have intercourse or whatever but the sperm doesn't' come out it goes into the bladder. Well [...] the way he spoke about it, it would be a definite side effect, but I couldn't understand why. [Mr Stone: allocated to laser, preferred TURP]*

One couple found that this had affected their sex life:

> *I says well we're past the children age so it's not going to make any difference, it's just a case of getting used to a different way, you know. I think that affects the men more than the women because it's something they have to come to terms with. It's their body that's altering. I don't know, that's something you'd have to answer that. But I mean... [Mr Pierce: allocated to and preferred laser]*

One patient was impotent. He had some symptoms prior to surgery, however, this got worse following treatment. He recalls that he tried to discuss this with the clinician on his follow-up visit, but did not feel that the clinican was interested in this problem:

I don't get erections any more. so it curtails, I've got a very good wife, don't take me wrong .....

Did they mention anything about impotence as a possible side effect?

They did mention that as a possibility, but at my age I'm not worried about impotence but I would have liked to have full use of the penis sort of thing, you know. But unfortunately since the operation I've got worse. I've got to .....since the operation erections are harder to get, so really there's no one I can talk to about it [...]all he [the clinician] was really interested in. Basically he just turned round and said are you all right, cos I didn't really gather that he wanted any more information [Mr Stone: allocated to laser, preferred TURP]

These men's beliefs about the trial and randomisation were examined in the light of their outcomes. It is interesting to note that the men who stated that their symptoms had been improved after treatment also incorporated trust and distrust within their accounts which were similar to those who had experienced complications or side effects as a result of treatment. However, this distrust may be of the method of treatment allocation itself rather than the trial.

Other findings

Diagnostic tests

A number of these patients found the tests involved in their diagnosis and the evaluation of their treatment painful and embarassing:

The extra tests, for instance they took biopsies of my prostate, I can tell you now that if I thought I had a similar problem and would have to have that biopsy again I would lie to avoid having to go through that again. I really would lie, not pleasant at all. Something I would've thought they should've done under anaesthetic. Like I say if that had been described to me by someone who had it, no way I would go through that again. I would honestly I think I would lie, say I'd got no problems rather than go through that again. It was painful, but it wasn't so much that as it was totally undignified, painful, uncomfortable. No, never again, I don't even want to think about it [laughs]. [Mr Grange: allocated to and preferred laser]

They put you through this test. I was watching it on the telly, where they, you could see it was turning in the inside and he was

taking pictures of your prostate and your bladder inside [...] But that wasn't nice, that wasn't nice, the pipes and all that was all right but when you see that thing you think oh my God! [Mr Symonds: allocated to CM and preferred active treatment]

The same with going out there to S_____ to the clinic afterwards because they give you the water tests again and when they put the tube down through the penis like you always feel that with you afterwards. I still sort of feel sore there you know [Mr Brown: allocated to and preferred TURP]

Well they're all right but I mean to say when they go up the front end and the back end with pipes and that and they do rather embarrass you and they leave you rather sore you know. But having said that if they tell you what they do you'd ...but hopefully as long as you'll be doing somebody some good. As long as it helps them for later on you know that's all that matters. [Mr Daw: allocated to CM, preferred active treatment]

It [pain after tests] lasted for about 24 hours because the end of the penis is sore and it's just sore right the way through but you know I know these things have got to be done so I mean it never worries me [Mr Stone: allocated to laser, preferred TURP]

Case studies

Each individual's narrative about trial participation was also analysed as a case study. This showed that most participants engaged in a dialogue to try and make sense of the trial design, their lay beliefs and their actual experiences of participation. Three examples described below have been chosen because they indicate a number of the different ways in which these men struggled to make sense of their knowledge of the trial and their experience of participation.

Similar recall of the trial and experiences of participation can produce different yet internally consistent accounts of participation. For example, this can lead to a belief that treatment should be individualised (Mr Watson) or that the clinicians were rationing treatments (Mr Symonds). Trust and distrust of the recruiting clinicians were common and Mr Haughton shows how participants incorporate trust into their accounts.

Mr Watson

Mr Watson, a 78 year old retired (retail) 'working class' man, was allocated to, and, indicated a preference for TURP, the *'standard'* treatment. He had some recall of randomisation, in that he knew about chance and the comparison of treatments:

> *Yes, but what it was, they took biopsies as well which proved that there was no cancer there or anything. But to improve down there I could take the option one option of three, to have an operation and what it involved was going in and a tube up your urethra and scraping the prostate. [Mr Watson: allocated to and preferred TURP]*

However he was adamant that he had not been allocated a treatment by *'lottery'*, because he did not witness anything to indicate that this had happened to him:

> *Int: So they didn't do that [randomisation/opening an envelope] with you?*
> *Oh no it wasn't a lottery sort of thing as far as I was concerned, no no. As I say it was in some of the information leaflets I got from the hospital saying that, but there was none of that. [Mr Watson: allocated to and preferred TURP]*

Because numerous tests were carried out, he believed that this had been used to inform his treatment allocation:

> *How did you choose the treatment from the three different options?*
>
> *Yes well I think it was based on the tests that they gave me and it was one of the types, I think this was for a scan on my bladder to see if it was empty and everything and [the recruiting clinician] came back and she says to us reading the notes and everything and what had happened up to then as regards my case, in their opinion as well the middle operation was the best option they thought. I mean naturally if I hadn't been in agreement with it I would have said right, no I don't want it, that's that [Mr Watson: allocated to and preferred TURP]*

This was further reinforced by comments made by the clinician on allocation:

> *Did they tell you much about the other options?*
> *Oh yes they were explained to us, but in their opinion this [TURP] was the better one for me, the other options was treatment with no operation, and the other operation was the*

> *burning of the prostate with laser and with that I think you came out within 24 hours with a bag and I think you had for about a week and then you went back. [Mr Watson: allocated to and preferred TURP]*

However, he received his treatment preference (TURP) and so was ultimately happy with the outcome, the treatment had proved successful.

> *How did you choose the treatment from the three different options?*
>
> *Yes well I think it was based on the tests that they gave me and it was one of the types, I think this was for a scan on my bladder to see if it was empty and everything and [the recruiting clinician] came back and she says to us reading the notes and everything and what had happened up to then as regards my case, in their opinion as well the middle operation was the best option they thought. I mean naturally if I hadn't been in agreement with it I would have said right, no I don't want it, that's that [Mr Watson: allocated to and preferred TURP]*

Mr Symonds

This is in contrast to the experience of Mr Symonds, a 59 year old man who worked in the manufacturing industry. He had been allocated to conservative management and after completing the trial received *'the common one'*, TURP, his preference. Treatment was successful, however, it 'took months' for him to fully recover. He went through a long struggle to make sense of the trial design, culminating in cynicism. He was sceptical of the use of envelopes and believed that it was a sham and that there was a hidden quota system in operation.

> *Now that's a thing, cos she says I was free to choose from didn't she. Now, eye, yes she gave us three, she says pick one of them. But I think along the lines afterwards, I'll be honest here, I'm dubious whether they are all the same. You know, you'll know for a fact that they're giving you the choice of picking one but you're saying to yourself, no matter which one you pick, you're not getting onto the other one. [Mr Symonds: allocated to CM and preferred active treatment]*

The information he had about randomisation proved problematic; he could not understand why envelopes were used. There was an element of suspicion within

this account, with the use of the envelope likened to a *'three card trick'*, which concealed a quota system:

> *It might be too expensive, they probably have to keep that I don't know. But I seem to think that the three card trick as we call it, it is a three card trick like. It doesn't matter which one you pick, I think it will be all the same like. You know I think you know you're going to get it. [Mr Symonds: allocated to CM and preferred active treatment]*

Perhaps surprisingly this distrust was scepticism of the method of allocation itself rather than the motives of the clinician. This deception was thought to be for his benefit. Although this is not explicitly stated, it may be that he believed the clinician wanted him to believe there was a fair and equitable method of allocation, when in fact, there was a quota system that delayed his treatment. He concluded that the clinician allocated him with the envelope *'only to keep you happy I think'*.

> *Do you think they decided?*
>
> *Yes, I think that, I don't know mind. But I think it's obviously they decide on what, what they've found out on examining you I think they decide which is going to be best for you. That's only to keep you happy I think.*
>
> *Some people have told me that they expected the clinician to give you a treatment specifically for your condition…*
>
> *Yes, I thought that, exactly, right. I thought they should tell you. That's why I think they do know by what they find out what is best for you, but they don't actually come out with that..... [Mr Symonds: allocated to CM and preferred active treatment]*

Perhaps the most crucial aspect was that Mr Symonds was not allocated to his preference. He expected active treatment and so individualised treatment allocation made the most sense to this participant. He did not understand why this did not happen:

> *So why do you pick, they may as well tell you what it's going to be. They may as well say well you're going to have this done this way and this is the process. You know, put it in a way that it's better for you in any case, it suits your condition then. I think that would be better than they let you take your pick when I think*

along the lines that you know you're being conned. [Mr Symonds: allocated to CM and preferred active treatment]

Mr Haughton

Trust and a belief in the clinician as expert, was often the basis for others' participation. For example, Mr Haughton who was a 70 year old retired (betting shop) man, had been allocated to TURP and indicated a preference for 'treatment', which was successful *'no bother'*. He had a good recall of randomisation, although his acceptance of this approach was linked to trust, in that he would accept whatever the clinician suggested, such as the trial.

I just wanted the thing over and done with. I didn't care too much how they did it as long as they did it. To be honest when you don't know what they are doing anyway, you are just quite prepared to take their word for it, certainly I am, happy to go along with whatever the expert recommends. That was it, we then went into the thing. [Mr Haughton: allocated to and preferred laser]

It is interesting to consider whether this respondent would have felt differently if he had been allocated to conservative management, the treatment option he did not want. As it was, he was allocated to treatment and expressed an altruistic desire to participate.

When _____ asked you to take part, has it been how you expected?
I think so yes. No looking at it logically, they poked around inside, discovered what was wrong and then they put it right in one of two ways, I didn't really consider the wait and see business and that's it, they've done just that. No, you know I'm quite prepared to accept the fact that these guys have to learn their profession the same as everyone else. You know it didn't inconvenience me so I was happy to go along with it. [Mr Haughton: allocated to and preferred laser]

Conclusion

Overall, most participants were able to recall some aspects of randomisation and what the trial involved. However, the majority also held other co-existing ideas about non-randomised methods of allocation such as rationing and

individualised treatment, which they used to understand and explain their treatment allocation. For a small number, altruism and an expectation of personal benefits were motivations for taking part. However, trust, distrust and their beliefs about fate and destiny developed as they tried to make sense of their treatment allocation in relation to their treatment preferences. The interview data and particularly the case studies illustrate the struggle that the participants engaged in to help them understand the experience of participation. Chapter 6 goes on to examine the experience of non-participation.

The experience of those who are eligible but decide not to participate

Introduction

This chapter will examine what happened to those patients who were eligible to take part in the trial but decided not to participate, including their motivations for deciding not to take part and their perceptions of the trial. It will go on to explore their recall of what the trial involved and how they made sense of the treatment they received and non-participation. These men's symptoms and their knowledge of the treatment available within the trial are also examined. Their outcome will not be examined because they received treatment outside of the ClasP trial. As for the participants, a number of case studies are also described to demonstrate the dialogue that most participants engaged in a to try and make sense of the trial design, set within their lay beliefs and their actual experiences of participation.

Characteristics of participants

Patients (n=11) were selected in order to reflect the main reasons for non-participation within the ClasP trial and were identified by the recruiting clinicians. Data on non-participation was recorded – it is important that trials record such information about those who are eligible but decide not to participate in order to reduce selection bias.

Thus those who according to the trial records decided not to participate because they had a treatment preference (5), did not want to be randomised to a treatment or take part in research (4), or did not want trial tests (1) were interviewed. One patient where no motive had been recorded was also selected. The labels used to link the quote to the non-participant include a brief description of their reason for this as recorded in the trial records. The sample

had similar characteristics to the participants. These men were aged 54-81 years old and were predominantly retired (Mr McCarthy and Mr Ladbroke were employed). The majority (8) attended clinic B and had not yet received treatment for their condition (7). Four had received the standard treatment (TURP) outside of the trial, one had received drug treatment and four were on the waiting list for surgery.

Previous or present occupation and the area in which they lived were used to broadly indicate these mens' social class. The majority of these men were categorised as working class and two (Mr Ladbroke and Mr Frame) as middle class.

Table 14: Non-participants

Name	*Age*	*Occupation*	*Reason for refusal within the trial records*	*Status*	*Location*
Mr Flynn	81	Textile industry	Preference	Waiting for treatment	B
Mr Maynard	67	Mechanic	Preference	Waiting for treatment	B
Mr McCarthy	54	Environmental Health	Preference	Waiting for treatment	B
Mr Allgood	78	Water Board	Randomisation	TURP	B
Mr Young	74	Building supplies	Travel	TURP	B
Mr Ladbroke	61	Manager	Randomisation	No treatment	B
Mr Becker	71	Catering	Refused tests	TURP	B
Mr Frame	69	Aeronautical engineer	'Refused', no reason given	Drug treatment	B
Mr Frost	66	Insurance	Randomisation /research	Waiting for treatment	B
Mr Gibbon	62	Coach driver	Preference	Waiting for treatment	A
Mr Williams	67	Bank	Preference	TURP	A

Reasons for attending the urology clinic

Symptoms

The majority of these men discussed the urinary symptoms they were currently or had previously experienced that had prompted them to seek treatment. The main symptoms were frequency, retention and nocturia. Many described how these symptoms had impacted on their lives. Only two (Mr Flynn and Mr Gibbon) gave no indication of the symptoms they had experienced.

Table 15: Non-participants' reported symptoms

Name	*Frequency*	*Hesitancy*	*Acute retention*	*Affecting sleep*	*Affecting social life*	*Other*

			/ retention			
Mr Flynn						
Mr Maynard		✓			✓	✓
Mr McCarthy			✓		✓	✓
Mr Allgood				✓		
Mr Young	✓		✓		✓	
Mr Ladbroke	✓	✓		✓		
Mr Becker			✓		✓	
Mr Frame	✓				✓	✓
Mr Frost	✓		✓			✓
Mr Gibbon						
Mr Williams						✓
TOTAL:	4 (36 %)	2 (18%)	4 (36%)	2 (18 %)	5 (45%)	5 (45%)

A tick signifies that these men discussed this symptom within the interview.

Retention

A small number of the men mentioned retention:

> *I never put it to prostate or anything like that and I didn't worry about it and it went away and I never had it for many years after. But I have occasionally got it you know, [...] you don't ever empty your bladder properly, so there's always some residue there so I suppose what happens is you've got this back pressure coming up. [Mr McCarthy: treatment preference]*

Two had experienced episodes of acute retention that required medical intervention:

> *But on the weekend on the Sunday it er just went into retention and there was er, I couldn't pass anything at all, it went on for about 10 hours and I thought well I'm getting a bit desperate here, so I phoned up in the morning and asked the doctor about it, if I could come over and see him and er he said the best thing to do is come straight over to the hospital. [Mr Young: travel]*

> *Had I been going over there like for months like some people they find it creeping up on them, unlike mine which come to an abrupt stop. [Mr Becker: refused trial tests]*

Nocturia

Nocturia, that is, the need to urinate often during the night, was a common symptom among these participants.

Yes I think it was, I can't remember how far back this was now, nearly six months ago perhaps I had been having some prostate problems for some while, not causing any great discomfort but the business of going to the toilet and not being able to do it that sort of thing and also getting up at all times during the night at one stage and not being able to go back to sleep again, so a lack of sleep. [Mr Ladbroke: a dislike of randomisation]

Well I didn't mind the operation because you see I wanted to get it done because I was living on my own here and nights when I wanted to go to the toilet it was sometimes more than 5 minutes before I could start to go and it was terrible yeah, yeah the pain [Mr Allgood: a dislike of randomisation]

Other symptoms

One patient discussed terminal dribbling:

Then the worst part of the lot which I did explain to them the worst thing really, the worst symptom I don't like is having gone to spend a penny you think you've finished and you're just walking away and you realise you haven't and you know that is embarrassing and that's the one symptom I would like to get rid of. [Mr Maynard: treatment preference]

A small number of the men mentioned frequency:

Yes well prior to going to S_____, what happened, I knew I was having prostate, you know, knew it was going on first of all because of my age and then of course I kept going to the toilet and... [Mr Young: travel]

Two patients spoke of their reduced flow:

It started about four or five years ago and what happened was I was having very slow flow of urine and not always emptying the bladder. [Mr Frame: no reason given]

Incomplete emptying with frequency was also problematic for one:

Well yes, I realise sometimes that the bladder doesn't empty but is that major? Is that a major problem, that's my point. I did say that the use of the bladder, just like last night, I didn't get up at all. Now I've been, had use of my bladder three times since seven o'clock. It's now half past 10. Maybe you could turn round and say that's excessive, I can't say. But it depends on, I mean this is my third cup of intake since then, so I don't know. It's what the

medical experts have to say not me. [Mr Frost: dislike of randomisation and research]

Affect on social life/normal daily activities

A number of men (5) described how their symptoms affected their social life and daily activities. They often described how they had to plan journeys and experienced anxiety finding public toilets:

> *It was a bit unsocial [...] Bit of a nuisance, yes you know I mean, if you went anywhere you'd think well first thing I've got to do before I go is go to the toilet and then when you get there you've got to make sure that there are toilets about like. It wasn't too bad but of course if you like a drink if you drink anything alcoholic that even makes it worse and that acts like a diuretic and makes it that little bit worse. [Mr Young: travel]*

> *I've not got to the stage where if I go on a coach journey I've got to make sure there are loos about and so on I do tend to get a bit concerned about that but there's people far worse than me, far worse than me. [...] But I go on some coach trips with some retirement people that are a little bit older than me and they all, most of the men and so on you know they've got to stop for the toilet, comfort stops or whatever, [Mr McCarthy: treatment preference]*

> *I wouldn't have put up with it for long term, even if I'd have to pay to, you know, I did say I've put up with it for I think it was nearly three months probably, I lived a full life admitted but I was fed up to the back teeth of it. [Mr Becker: refused trial tests]*

> *I knew where and how long I was going to be out for and there would be no problem with toilets that sort of thing. [Mr Frame: no reason given]*

As for the participants, such experiences were often 'embarrassing' for these men:

> *I mean they may say it's not serious but to me it's quite embarrassing it does interfere with your life and I mean if I go out for an evening I've got to be very careful how much I drink and now if I go to a skittle match, where I would probably drunk two pints of shandy or something like that or a pint of beer and perhaps a shandy I now think I'll just have a half please and I try and make that half last because if I don't then I'm in and out of bed all night you know. [Mr Maynard: treatment preference]*

Well I've got nothing to compare with other than the symptoms I have I know are embarrassing to me, I've put up with them for a couple of years with tablets and the tablets didn't seem to be having any further effect then you know it got me to a stage and then I seemed to be static and I had problems which I explained and I was a bit disappointed that those problems are still going to be with me. You know I thought well I thought all this was going to put it right. [Mr Maynard: treatment preference]

It gradually got uncomfortable in as much as it was embarrassing when I sometimes went into town with my wife to do some shopping and I've got to find a toilet quick, that sort of thing [Mr Frame: no reason given]

Knowledge of the treatments available within the trial

These men displayed a low level of knowledge about the three treatments available within the trial: TURP, laser and conservative management. The information levels within this group are probably comparable to ordinary men who receive 'normal' treatment for this condition. None of these men appeared to have any knowledge of what conservative management involved.

Knowledge of TURP

A small number of men (4) could recall that TURP was the standard treatment for this condition:

Well I think me being me, if the TURPs is the standard one then I'm quite happy thank you because that's been proven with everyone else [...] Well I suppose it's run of the mill treatment. [Mr Gibbon: treatment preference]

A small number of these men also recalled that this method involved 'cutting':

What had they told you about the operation?

They told me what it would entail, you know that they took this erm probe thing up with a cutter on it or something, it's a light and a cutter I think something like that and they take off the prostate and er so in the end I went up and had it done and it worked out very well. He said, you know that there could be snags but it went very well. There was erm, no I don't suppose there was really any pain you know, not any excessive pain and only a little bit of discomfort anyway. [Mr Young: travel]

No he didn't say what they were going to do, he just said that they would perform to remove, like coring an apple, my prostate gland, that's all he said. [Mr Becker: refused trial tests]

Knowledge of laser therapy

Although eight of these men mentioned the laser therapy, only three (Mr Williams, Mr McCarthy and Mr Frost) were aware that this was a new treatment and only one (Mr Williams) knew that this involved a catheter bag:

It's in its infancy [Mr McCarthy]

The level of knowledge about all the treatments, particularly conservative management, is very much lower among these non-participants compared to the participants. Although it was likely that they were given the patient information leaflet, it would seem that they were not able to recall more than very basic matters.

Recall of randomisation

As for the participants, non-participants' recall of the trial can be broken down into six integral elements: an understanding of the involvement of chance, that their treatment allocation was concealed, that envelopes were used to allocate treatments, that treatments were being compared, the existence of clinical uncertainty and that they were being asked to participate in an experiment.

As can be seen from table 16 below, all but two non-participants (Mr Flynn and Mr Allgood) could recall some aspects of trial design. As for the participants, their recall was often expressed in a number of different ways. Overall this group had a lower level of recall of randomisation than the participants, although surprisingly, almost all could recall the experimental nature of the trial, compared to only half of the participants.

Age and time after they had been approached to participate appeared to have had no influence on these men's recall and understanding of trial information. The influence of social class was also examined. The two 'middle class' men had

varying levels of recall and understanding of these six elements, ranging from the second highest (Mr Ladbroke) to one within the middle range (Mr Frame).

Table 16: Recall of randomisation

Non-participants	*Chance*	*Comparison*	*Envelopes*	*Concealed allocation*	*Experiment*	*Clinical uncertainty*
Mr Becker	✓	✓	✓	✓	✓	✓
Mr Ladbroke	✓		✓	✓	✓	
Mr Maynard		✓		✓	✓	✓
Mr McCarthy	✓	✓			✓	
Mr Young	✓				✓	✓
Mr Frame		✓			✓	✓
Mr Frost					✓	
Mr Gibbon					✓	
Mr Williams					✓	
Mr Allgood						
Mr Flynn						
TOTAL:	4 (36%)	4 (36%)	2 (18%)	3 (27%)	9 (82%)	4 (36%)

As for the participants in the previous chapter, a tick in table 15 signifies that the informant discussed that particular concept and that he demonstrated that he understood the concept in the way it was presented in the study information.

Chance

Four non-participants (Mr McCarthy, Mr Ladbroke, Mr Becker and Mr Young) could recall that chance was involved in the way treatments would be allocated within the trial.

> *Yes he did list for me, outline the various different methods, that's right, and explain to me that your particular case would be treated by lottery if you like, by picking up an envelope and that was to be it. [Mr Ladbroke: a dislike of randomisation]*

As for the participants, lay descriptions were also common within this group. For example, *'lottery'* (Mr McCarthy and Mr Ladbroke), *'balls in a cup'* (Mr McCarthy) and *'luck of the draw'* (Mr Young and Mr Becker) was used to describe randomisation:

> *I mean I think you know they said you know, if the laser side of it is still in its infancy, it's not one hundred per cent then I would say no, well yes you can have this but we can't guarantee the results, OK, you know where you stand, not just to say well you know we'll just put balls in a cup and get whatever comes up. No, I'm not happy about that. I'd like to know what's, what I'm being offered, 100%, one way or another. [Mr McCarthy: treatment preference]*

However, such descriptions of chance, such as 'lottery' and 'luck of the draw' also integrated fate and destiny, comparable to the participants' accounts. For example, Mr Becker appears to believe that some participants will be 'lucky' and receive the 'right' treatment within the trial:

> *It was the luck of the draw, which is why you had two envelopes, you've got to pick your choice. [Mr Becker: refused trial tests]*

Concealed allocation

Three non-participants (Mr Ladbroke, Mr Maynard and Mr Becker) were aware that allocation to a treatment within the trial would be concealed. For both, this was linked to their awareness of the use of envelopes.

> *You will be allowed to pick an envelope and one will say laser and one will say surgery. Whichever you pick you'll get. [Mr Becker: refused trial tests]*

Two were also aware that this also involved concealment from the clinician:

> *He explained that there would be no specific method of treatment given, that they would be done by opening envelopes or something to decide 'ah this is the method for you' or whatever and if it happened to be operation then you should bear in mind that 1% die. [Mr Ladbroke: a dislike of randomisation]*

> *He said 'quite frankly I don't know which is the best way. [Mr Maynard: treatment preference]*

Comparison of treatments

Four (Mr Maynard, Mr McCarthy, Mr Becker and Mr Frame) were aware that the trial involved the comparison of treatments:

Because they were running it to see which was the best result, laser or surgery and you agreed to take part in it. [Mr Becker: refused trial tests]

This also involved the testing of treatments:

I can only imagine that it would mean going to the hospital with a group of people. Say there were ten people involved, if there were two tests, five would do one, five would do the other. If there were a different number of tests, if it was three tests there would've been twelve people, four would've done one, four would've done... something of that sort. It would've probably have meant keeping you in hospital for at least over one night. Though not necessarily, no I'm not sure about that, but you would have to go by whatever requirements they had about abstaining from certain foods for certain times if necessary and I don't really know more than that, I'm guessing. [Mr Frame: no reason given]

Clinical equipoise

The information sheets indicated that the clinicians did not have a treatment preference and that the three treatment options within the trial were equivocal. Four of the non-participants (Mr Maynard, Mr Becker, Mr Frame and Mr Young) could recall such uncertainty about the treatments within the trial. This is surprising, as less than a third (6) of the participants could recall this feature of the trial.

This was often expressed as a belief that the treatments within the trial were equally effective:

I think I would have thought well either have it cut out or have it lasered out. It wouldn't make no odds as long as it does the job. Yeah, I mean I wouldn't have, I don't think I would have minded either way there. [Mr Young: travel]

Thinking back to when the nurse came to see you about the trial...how did you feel about that?

Well actually you get so brassed off with having the catheter up there you don't care what they did as long as they got you out of the predicament that you are in. Whether they did it by surgery or laser it doesn't matter. [Mr Becker: refused trial tests]

An acceptance of clinical equipoise is linked to trust. This will be discussed in more detail below:

> *How would you feel about your treatment being chosen by randomisation rather than…*
>
> *Well I wouldn't be worried about it because anything that the national health service is going to offer is obviously based on experience which is going to be satisfactory over the range of surgery requirements or types which are available. If something was quite unsuitable it would never have been included in the random method of tests. [Mr Frame: no reason given]*

The differing rationalisations of clinical equipoise were sometimes an element within their rationale for not participating. This will be discussed further below (pp.). For example, Mr Frost does not believe that different treatments can be equivocal for all patients and that one treatment may be more likely to benefit a particular patient:

> *You can't have a like for like because two patients can be altogether different [Mr Frost: dislike of randomisation and research]*

Participation in an experiment

Almost all (9) were aware that the trial was some sort of experiment. This was often expressed in lay terms such as 'guinea pig' (Mr McCarthy, Mr Ladbroke, Mr Becker and Mr Frost):

> *Going back to the trial for tablets, how do you feel about being part of a trial?*
>
> *Well in other words I was being used as a guinea pig. Yeah, I don't mind that no, no. [Mr McCarthy: treatment preference]*

> *Well all they were doing at that moment in time, they were doing so many with surgery and so many with laser and they were using people like guinea pigs too. [Mr Becker: refused trial tests]*

> *Well I suppose my initial reaction to that is that I might be at risk a little bit in being a guinea pig. [Mr Ladbroke: a dislike of randomisation]*

It may be that such knowledge was a factor in their non-participation.

Involvement in research

These non-participants often held a partial knowledge of what a trial actually involved and these are similar to the descriptions given by participants. For example, two (Mr Young and Mr Becker) described the trial as a 'survey':

> *So when the nurse said there are these two options and these two envelopes, what did you think?*
>
> *I thought well, it was a survey. If you entered their survey then this is what they did when you were nearer the operation. [Mr Becker: refused trial tests]*

The trial was often believed to be tests (Mr Frame and Mr Williams):

> *I would've agreed to say I'm perfectly happy to take part with any form of randomised treatment but whether it was going to be a trial test or whether it was to be the final test I wasn't aware. [Mr Frame: no reason given]*
>
> *Why did you prefer the operation?*
>
> *It just seemed quicker like. I mean they took us on a Thursday, done it on a Friday, took the catheter off on the Saturday, I could've come home on the Sunday but I couldn't get transport, so I came home on the Monday and it was finished. I just thought with the laser, getting it and carrying the bag. I wouldn't have minded the tests, it was just carrying the bag. [Mr Williams: treatment preference]*

It was also described as a questionnaire to assess symptoms. This is comparable to the beliefs of some participants that the trial would merely entail additional paperwork:

> *Did they ever mention what being part of a trial would mean?*
>
> *Not a lot of detail no. I suppose the trial, the paper I was completing, was more or less self explanatory dealing with nothing else but symptoms. [Mr Maynard: treatment preference]*
>
> *I assumed from that that the degree of the symptoms that I'd had according to that paper would sort of indicate to somebody well perhaps this would be the best for you, whatever that's what I expected, but that really isn't what happened. [Mr Maynard: treatment preference]*

Lay understanding of trial terms

As with the participants, non-participants similarly gave a lay description of random as an event with no purpose:

> *So any one of those random things would therefore be successful and it wouldn't have worried me at all. [Mr Frame: no reason given]*

The trial was also believed to be the process of trying out a new treatment (Mr Maynard, Mr McCarthy, Mr Young and Mr Frost):

> *I was referred to him for the prescription for the [tablets], which I thought was a trial, I don't know what they call it. They try you out on it and if it works OK and if it doesn't you know. [Mr McCarthy: treatment preference]*

> *So what were your expectations?*
>
> *Well I thought, I thought it might be a trial of tablets, drugs, because I've got a brother who's got it, he also has Parkinson's disease and he said they put him on drugs and I thought well it might be that you know. [Mr Young: travel]*

Three (Mr Maynard, Mr Gibbon and Mr Williams) non-participants rationalised that the standard treatment could not be part of the trial because it was already in use. This is similar to the interpretation of one participant (Mr Bowler).

> *You filled out the questionnaire...*
>
> *Well that's what I assumed, I thought well if you are of this opinion and you've looked at my records and you've spoken to the consultant, I thought well perhaps I have got wrong. I thought the laser was a standard treatment as well. [Mr Maynard: treatment preference]*

> *Well I think me being me, if the TURPs is the standard one then I'm quite happy thank you. [Mr Gibbon: treatment preference]*

Pathways to refusal

Despite the fact that the majority could recall being asked to take part in an experiment, these non-participants had distinct beliefs about the treatment they recedived. This is part of the process of making sense of their experience of being asked to participate and the treatment they received. Of the eleven non-participants (based on information contained in the trial records), three believed that they had agreed to participate in the trial and only five believed that they had made an active decision not to take part in the trial. The remaining three had no recall of being asked to participate.

Table 17: Pathways to refusal

Knowledge of the elements of randomisation	*Name*	*Reason for refusal within the trial records*	*Active refusal*	*Believed they had agreed to participate*	*No knowledge of the ClasP trial*
6 (maximum)	Mr Becker	Preference		✓	
4	Mr Maynard	Preference		✓	
4	Mr Ladbroke	Preference	✓		
3	Mr Young	Randomisation	✓		
3	Mr McCarthy	Travel		✓	
3	Mr Frame	Randomisation			✓
1	Mr Frost	Refused tests	✓		
1	Mr Gibbon	'Refused', no reason given	✓		
1	Mr Williams	Randomisation / research	✓		
0	Mr Allgood	Preference			✓
0	Mr Flynn	Preference			✓

Active refusal

Five non-participants (Mr Young, Mr Ladbroke, Mr Frost, Mr Gibbon and Mr Williams) appear to have made an active decision not to take part in the trial. This group all had a good recall of the trial in terms of experimentation, however, only two were aware of the involvement of chance (Mr Young and Mr

Ladbroke) and the additional presence of clinical uncertainty (Mr Young) and the use of concealed allocation (Mr Ladbroke). These men were 62-74 years old and had attended both trial centres. One (Mr Ladbroke) was categorised as middle class.

According to the trial records these patients decided not to take part in the trial because they had a treatment preference (Mr Gibbon and Mr Williams), the travelling involved would be difficult (Mr Young), did not want to be randomised to a treatment (Mr Ladbroke) or take part in research (Mr Frost).

This group also incorporated a number of additional reasons for not taking part in the trial within their accounts. They all additionally cited a dislike of randomisation and trial participation, three preferred to receive individualised treatment and two expressed high levels of anxiety about the trial and their treatment.

Table 18: Reasons for active refusal

Non-participant	Treatment preferences	Preference for Individualised treatment	Trial/ randomisation	Time/ travel	Anxiety
Mr Young	✓	✓	✓	✓	
Mr Ladbroke	✓		✓		✓
Mr Frost	✓		✓		
Mr Gibbon	✓	✓	✓		✓
Mr Williams	✓	✓	✓		

Treatment preferences

All five (Mr Young, Mr Ladbroke, Mr Frost, Mr Gibbon and Mr Williams) expressed a treatment preference. The majority (Mr Young, Mr Gibbon, Mr Williams) indicated that they wanted TURP because they believed this to be the standard and possibly the most effective treatment:

> *Well I think me being me, if the TURPs is the standard one then I'm quite happy thank you because that's been proven with everyone else. Having said that I appreciate someones got to do,*

you've got to have someone for research and all that. But me worrying, no thank you, [Mr Gibbon: treatment preference]

Just that, they told us that the bladder wasn't quite empty after passing water and asked us if I wanted laser treatment or the ordinary one, but I didn't like that. I just preferred the ordinary one she said you'd have to carry a bag [catheter] about, that sort of thing and I didn't fancy that. [Mr Williams: treatment preference]

This decision was sometimes based on a preference for a less invasive treatment before having surgery:

I was a little bit surprised when the gentleman said [about CLasP], gave me the information that it's self explanatory type of thing what was discussed. I don't particularly like the thought of having, if there is surgery involved because erm it's not always certain if there is a problem it will eradicate the problem. I mean this man said to me as I say about the tablets he said, I haven't been to the hospital, my GP has given me these tablets and if the tablets don't resolve any difficulty or problem there... [Mr Frost: dislike of randomisation and research]

If you had a free choice, what kind of treatment would you have wanted from them?

Well I suppose what I, I would've wanted to be told, your condition is all right, you take these tablets and the tablets will improve your prostate gland trouble or at least try them before considering any of the other methods. I mean I think perhaps I wanted to try that course of action before considering anything else, that's what I thought, that's the way my mind thinks anyway, lets go for the soft option first and if that don't work, well we'll have to consider one of the other way of going about it. [Mr Ladbroke: a dislike of randomisation]

This was associated only with wanting a 'successful' treatment:

The thing is to my way of thinking erm it's either one form of treatment or the other on this and neither form of treatment are totally 100%. So there's no point in having something which isn't 100% to my way of thinking. [Mr Frost: dislike of randomisation and research]

Preference for individualised treatment

The decision not to participate was often made because they received no direction from the clinician as to whether they should participate in the trial or

not. For example, Mr Young explicitly asked for advice and in response to receiving no direction from the clinician and he decided to have the option he knew most about, the standard treatment (TURP):

> *When he said 'well its entirely up to you' he didn't seem to want to make any decisions or choices for me and so I said well I thought the easiest option, the thing is to go for the operation because I've been told about it before you know, I've been up there a couple of times to see Dr T_____. [Mr Young: travel]*
>
> *How did you feel about saying that you preferred the operation?*
>
> *They didn't put no pressure or owt on us. They just asked us, told us the alternative and what they were like and asked us which one do you prefer and I tell her like and she said well the laser one is, I'll go no further because they wanted tests and that but they didn't mention that at first. [Mr Williams: treatment preference]*

Mr Gibbon believed that his recruiting clinician had directed him towards one of the treatment options. This was seen in a positive light: sensing his uncertainty, the recruiting clinician had directed him away from trial participation:

> *They did an ultrasound there and then and they give me this leaflet on various treatments for prostate problems and asked about the new laser treatment I think and this [recruiting clinician] explained with little diagrams and things and explained what this process would entail [...] I really worry badly. So when [the recruiting clinician] tells me this I must have changed, I must have, because I was a bit taken aback by that, I wasn't expecting this to be honest. I thought it was 'here take these pills you'll be OK', so me face changed and she says what do you think about this laser you know and explained it and as I said I think my face must have changed and then [the recruiting clinician] said I don't think this is for you, I don't think it's in your best interest for you to, and I agreed and said no I don't think it is. So then [the recruiting clinician] said Oh well you'll be referred onto Mr ___ waiting list for, I forget, I think it's TURP's or something, which is the normal. [Mr Gibbon: treatment preference]*
>
> *I more or less went by guidance from [the recruiting clinician], [the recruiting clinician] said about this and I said yes that sounds lovely and as they explained it on [date] it was [the recruiting clinician] that noticed more or less the change in me. [Mr Gibbon: treatment preference]*

In contrast, Mr Ladbroke felt pressure to participate in the trial and infers from this that the clinician was having trouble recruiting patients, and thus rejected the trial:

> *How about monitoring and no treatment?*
>
> *Well no he didn't mention that but that seems to be what's happening with me. But then, I found him a little bit pushy actually.*
>
> *So how did you feel about that?*
>
> *I said give us the pills, I thought I'll have the pills thank you very much! (Laughs)*
>
> *Why do you think he was so keen to have you on the trial?*
>
> *I've no idea, no idea. He was definitely, yes he gave me the impression, perhaps wrongly, that he was er having trouble getting anyone submitting themselves to the trial (laughs). I think he was determined to get somebody to volunteer, he gave me that impression (laughs). [Mr Ladbroke: a dislike of randomisation]*

Mr Frost found it hard to ask the recruiting clinician what the trial actually involved:

> *I wondered whether it was an experiment to be funded by someone. Erm, it's was difficult to ask that man point blank, is it clinical research. [Mr Frost: dislike of randomisation and research]*

It is interesting to note that even when these patients had what appeared to be different levels of direction from their clinician, this can lead to a similar outcome, the rejection of the trial.

The trial and randomisation

All five of this group cited some aspect of the trial design in their reason not to participate. Almost all (Mr Young, Mr Frost, Mr Gibbon and Mr Williams) wanted the 'right' treatment. This was often based on a misunderstanding of clinical equipoise and the belief that the standard treatment would be more effective:

> *I mean in all forms, if it's going to be surgery, all right surgery has got to be positive, there's no point to my way of thinking to having some surgery if the problem isn't eradicated. [Mr Frost: dislike of randomisation and research]*

But me worrying, no thank you, I'll stick with the one that's tried and tested if it's all the same you know. That is my way. [Mr Gibbon: treatment preference]

A dislike of being part of an experiment was a factor for Mr Ladbroke and Mr Frost:

How would you feel about that?

A little bit uneasy

In what way?

Well, I shall I say, I don't want to be used for experimental purposes. If it's going to be, have to be surgery, I want the surgery to be successful. [Mr Frost: dislike of randomisation and research]

I can see the reasoning behind it all, sensible enough, things that you know, we all want to learn and improve, I can understand that. But at the end of the day if the individual doesn't want to be forced down one particular route, he shouldn't be. But I can understand. [Mr Ladbroke: a dislike of randomisation]

This was linked to not wanting to become a 'guinea pig' (Mr Ladbroke and Mr Frost):

Obviously I think I was taken aback a bit about being offered to be a guinea pig, and to go into this trial and that threw me. So had I been, had I known about that before I went I might not of been thrown off balance as much. But I was, but he did outline the alternatives to me, yes [...] that smacks of, smacks of possibly receiving some sort of treatment that hasn't been properly researched, that was it. [Mr Ladbroke: a dislike of randomisation]

Well I felt the gentleman explained what he had written down, now my point about it is this. Is this [CLasP patient info sheet], how shall I say, an experiment? Is this an experiment that is possibly funded by the University of B___ and the University of A____ or patients? Is this gentleman one of a team? Is it a research into prostate which the University of A____ and the University of B____ will fund on a patient basis? That wasn't explained and its a little bit difficult to come out and say right doctor, am I a guinea gig? [Mr Frost: dislike of randomisation and research]

A dislike of the involvement of chance in their allocation to a treatment was also present:

What did you think of that? Instead of them saying 'this is the best treatment for you' they said 'we're going to open an envelope to decide'?

No, I didn't like that I must confess, no I didn't like that (laughs). I wasn't in control of anything then was I, you're not in control (laughs). No I don't think so no, not being able to consider yourself, consider the methods and design for yourself, what you would like with the help of the doctor, er is yes out of control. [Mr Ladbroke: a dislike of randomisation]

However, three (Mr Young, Mr Ladbroke, and Mr Williams) of these patients who appeared to be making an active decision not to participate in the trial because it involved experimentation and randomisation, also stated that this was not the main factor for this decision. For example, Mr Williams asserts that he was not concerned about the trial, he just did not want surgery, specifically because laser involved having a catheter bag:

It wasn't the tests that I was worried about it was just the bag. I thought it was going to be a bit awkward and that like. [Mr Williams: treatment preference]

Sometimes, the condition itself improved, so that treatment was no longer required:

Did that put you off the operation?

Yes, I suppose it did, I suppose it did er, but having said I mean if they can just, If I'm being serious and demanded an operation then obviously I would have to go along with that. But I mean the way its been described to me, that there were other, what I would call, harmless treatments that could rectify the condition and just thinking about it now, knowing that you were coming today Katie, I was thinking about it now, ever since, I don't know whether this is up here (points to head) or not, but ever since I'd been and had that examination by that consultant at S_____ the situation would appear to be a little better. Aye, whether that's just me or not, no I don't seem to be bothered as much. I'm not saying that the symptoms aren't there every now and again but certainly not as frequent as it was before. I would have thought on balance it's, the situation is better, yes. [Mr Ladbroke: a dislike of randomisation]

The practicalities of participation

One non-participant (Mr Young), based his decision to refuse on a (valid) assumption that the trial would be more time consuming than the standard treatment:

> *They said something about a new treatment. He went all through the notes and he said well I am running a sort of a section of people with prostate to... I don't know what the treatment was, he didn't tell me anything about it. No he didn't tell me anything about it, he said you know, you can come or whatsname...but my trouble was not so much the, I wasn't worried about what the treatment was, I didn't know what it was. I thought to myself, coming from C_____ I had to arrange transport you see and so it means getting a car up, people waiting for me and so I didn't know if it was let's say a weekly treatment it would mean going up for probably a matter of months, weekly and he didn't sort of say too much about it and in the end he said well it's up to you entirely. [Mr Young: travel]*

Anxiety

For two non-participants (Mr Ladbroke and Mr Gibbon), their decision was linked to their anxiety about trial participation:

> *Of course, I admit I'm a terrible worrier, I am, I really worry badly. [Mr Gibbon: treatment preference]*
>
> *What did you think of the operation after he had said that?*
>
> *I thought to myself well I'm not in any pain, I thought I'll have the pills I think. The coward's way out perhaps, I don't know, but that's the way. [Mr Ladbroke: a dislike of randomisation]*

Believed they had agreed to participate in the trial

Surprisingly, a number of patients who according to their notes were non-participants (Mr Maynard, Mr McCarthy and Mr Becker), believed they had agreed to take part in the trial. All of this group could recall experimentation (Mr Maynard, Mr McCarthy and Mr Becker), randomisation in terms of comparison (Mr Maynard, Mr McCarthy and Mr Becker) and clinical uncertainty (Mr Maynard, Mr McCarthy and Mr Becker). Fewer were also able to recall chance (Mr McCarthy and Mr Becker), concealed allocation and the use of envelopes (Mr

Becker). These men were 54-71 years old and had all attended clinic B. All three were categorised as working class.

There was a disparity between these patients' interpretation of what had occurred during the consultation and what had been recorded in the patient trial records. Two (Mr Maynard and Mr Becker), were willing to participate but believed that the clinician had excluded them from the trial, while Mr McCarthy did not believe that he had 'refused'.

Table 19: Reasons for the belief that they agreed to participate

Non-participant	Directed by recruiting clinician	Lay interpretation of trial	Agree to participate in anything	Altruism
Mr Maynard	✓	✓	✓	
Mr McCarthy	✓	✓		✓
Mr Becker	✓	✓	✓	

Directed by the clinician

All three believed that they had been directed towards (or away from) one of the treatment options by the recruiting clinician:

> *I never had a lot of choice. The same as she said that if it fails you have to have a catheter, but as you've already got one you've got no choice, you're going to go for it aren't you. I said oh yeah. [Mr Becker: refused trial tests]*

> *So I brought this up with the consultant and the consultant I spoke to at the time he said 'we have been using it but we don't think a lot of it because its in it's infancy and its you know, there's a lot more work has to be done', research and so on. [Mr McCarthy: treatment preference]*

> *The first thing that was offered was the laser, I said yes please and the next minute it was whipped away and then an operation and I said yes again you know. What I'm looking for is something to put it right [...] Well he seemed to have his mind made up as I went in his room. [Mr Maynard: treatment preference]*

Two (Mr Maynard and Mr Becker) had expected to participate, but believed that they had been excluded from the trial. This is similar to the participants' beliefs about rationing.

> *Because when it said about I didn't, in your letter you said about the trials, I didn't have a chance. [Mr Becker: refused trial tests]*

> *I assumed that really, that was really what more or less I was doing with the tablets, that's what I assumed. The second one was straightforward laser and er I assumed that a laser would do er something similar to what they would do under an operation and I mean I'm not just, we didn't go into that sort of detail so I don't know but well I shall just have to wait and see I suppose now. But I did think that you were under the wrong impression when I received this (my letter) that I had not agreed to go through, take part in the... [Mr Maynard: treatment preference]*

There is an element of distrust within their accounts, which will be discussed below.

These two non-participants (Mr Maynard and Mr Becker) would appear to agree to receive any of the available treatments and appeared to be willing to accept trial participation. For example, Mr Maynard appears to agree to both laser and TURP as the recruiting clinician presents them to him:

> *Then he went on to say to me that he expected it to be more serious perhaps than it was and that would I be interested in a laser job? I said that would suit me fine. So he went, he left the room and went out, spoke to someone, came back in and said 'well it appears that it's not bad enough for a laser job' So I said well OK. So then he surprised me again and said 'now I can still put you down for an operation' So I said 'well, OK'*

> *In the notes it stated that you would prefer the operation...*

> *No that's not correct at all, I accepted what was offered to me. I was prepared to accept anything that was offered to me. [Mr Maynard: treatment preference]*

> *I think you get to the stage where you don't care what they do as long as you get one. [Mr Becker: refused trial tests]*

This is very similar to the experience of the participants (see previous chapter).

Understanding of the trial

Non-participation within this group appeared to be unintentional. The belief that they had not refused may be associated with their lay interpretation of the trial. For example, to try something out:

> *Whatever, I just sort of said oh there must be something they're trying out. [...] So as regards to, I wasn't ever aware that I had refused to take part in a trial, I assumed that this investigation and the taking of this tablet F____ was part of some sort of trial that's all I can tell you really. [Mr McCarthy: treatment preference]*

> *He spent some time explaining the situation, that there are three, roughly three ways of dealing with the problem,[...]and 'we will talk though your trial when you complete it [questionnaire]' which was what I expected to happen. [Mr Maynard: treatment preference]*

The use of questionnaires also appears to be a factor. Both Mr Maynard and Mr Becker assumed that their completion of the initial symptom questionnaire was the first stage of trial participation:

> *I thought I was participating in the trial. In fact, he went on to explain to me that the trial was nothing to do really with the hospital, it was something which was tied up with the University and he gave me the questionnaire. I brought it home- in fact it took me quite some time to complete it, and then having completed it, I went back and amended it a couple of times because I thought well there's more than one answer to these questions and erm I amended a couple. So I thought I has taken part in the trial. [Mr Maynard: treatment preference]*

> *She came and said would you like to fill this out so I said, it was a great big form and saying what, how it was affecting you. Well it was too late, I had a catheter in and it was all in the past. So she said would you fill it in what it was like, well I said, I was all right before you know, I just had[Mr Mills: allocated to CM, preferred active treatment]*

However, a few participants found their allocation to conservative management difficult to accept. Despite being able to recall the involvement of chance in their allocation, these participants also wanted and expected 'treatment'. This was

often interpreted as their exclusion from treatment and this was often upsetting for these pateints.

> *You know at the moment, as I said like, the problem with this water trouble is you know four or five times every night and it's a bit annoying you know. I can go to the toilet, come downstairs and within a matter of minutes I've got to rush back upstairs. Well I think something ought to be done about it. [...] It was, it was because it was like, I naturally thought that they were going to do something about it but as I said I had no tablets or nothing for it, so that's all I can tell you. [Mr Jamison: allocated to CM but preferred active treatment]*

> *a sudden chomp it was stopped, so she said fill it out what you can. So I filled it out and then they sent for me for the interview to go and see the specialist and I took it with me and he said well that's a bit late isn't it and promptly threw it away. [Mr Becker: refused trial tests]*

For one (Mr Becker), the use of envelopes was an important factor. He believed that he had been excluded from the trial because he had an expectation of, but did not see, an envelope being used to allocate him to a treatment:

> *Well what they did, when that [recruiting clinician] was there [...] said if you partake of this, this survey you will fill this out and then come and see us and then you will be given an envelope. [...] Well it never happened. [Mr Becker: refused trial tests]*

This is very similar to the rationalisations of those who actually participated. The absence or occurrence of certain anticipated trial events led some participants to conclude that they had not been randomised to their treatment. However, for non-participants, this may have led them to believe that they had actually participated in the trial.

Non-randomised methods of allocation

Despite their knowledge of the trial and randomisation, this entire group also believed that non-random methods of allocation were not inconsistent with trial participation. This may have led to their exclusion from the trial.

Mr Maynard had an expectation that the clinician could individually allocate him to a treatment within the trial:

> *The surgeon did say, I take it he was a surgeon anyway, he did say that all three methods really are quite OK and they are quite happy with all three methods but er you know what suits some may not suit necessarily suit someone else. So and the impression I got was that it would be as a result of talking to me about it before it was decided. [Mr Maynard: treatment preference]*

There was also an expectation that they could decide which of the treatment options to receive:

> *Well I self allocated to the watch and wait. Of course they did mention the main side effects, well of course the main side effects is that you can become sterile. Well that doesn't worry me because I'm not married now and I'm not particularly thinking about a family or anything, I've not got any family, it's just something I accept in the same way as I can't understand IVF, why people can't accept it, there are more important things that can go wrong. But that's the position with me, watching and waiting, sort of putting it off I suppose, I don't know. [Mr McCarthy: treatment preference]*

Mr Becker appears to believe that he is still eligible to participate in the trial even though he had refused to consent to a diagnostic test for cancer. This would not have excluded him from the trial:

> *So all in all, I didn't refuse to partake of anything. The only thing I did refuse, when I saw him he did say would you like to come in for a biopsy so we can see what we are going to do or if you want to go straight in. I said I want to go straight in said, I'd have it done now if I could. [Mr Becker: refused trial tests]*

Such beliefs that individualised treatment allocation is not inconsistent with trial participation are similar to the beliefs of some participants.

Acceptance

Willingness to accept trial participation can also be seen in their expectation of receiving personal and altruistic benefits. However, only Mr McCarthy, who believed he had agreed to participate in the trial, did so for altruistic reasons:

> *But I like to know you know and I can manage the problem better, but also I think this research is a very good thing to help the medical side of things, it helps other people . But I just manage it I do the right things. [Mr McCarthy: treatment preference]*

No knowledge of the ClasP trial

Three patients (Mr Flynn, Mr Allgood and Mr Frame) had no knowledge of this particular trial and could not recall being asked to participate. It is interesting to note that these patients have very different levels of recall of experimentation and randomisation. Although both Mr Flynn and Mr Allgood have none, Mr Frame (an aeronautical engineer) has a clear understanding of experimentation and randomisation in terms of chance, comparison of treatments and concealed allocation. Given his level of knowledge, one might expect him to recall being asked to participate in this specific trial. These men were 69-81 years old and had all attended clinic B. One, (Mr Frame) was categorised as middle class.

Table 20: Reasons for non-participation

Non-participant	No recall of the trial	Directed by the clinician	Agree to anything	Altruism
Mr Flynn	✓	✓	✓	
Mr Allgood	✓	✓		
Mr Frame	✓	✓	✓	✓

Directed by the recruiting clinician

All three believed that they had been directed by the clinician towards one treatment:

> *They didn't think it was severe enough or..?*
>
> *Well it was about right I think but erm he said that I think it would be best if you didn't go in for it, so I left it like that. Now I've got to go again in September so I don't know what that's for...and I had a scan about a month ago. [Mr Flynn: treatment preference]*
>
> *Was that (trial treatments) ever mentioned by anyone else?*
>
> *No, no that's all he told me, he said that's what we got to do yeah that's how your operation will be. The other way we cannot do it so he said 'that's what you'll have to have done'. [Mr Allgood: a dislike of randomisation]*

This may be associated with having a treatment preference. For example, Mr Allgood appears to have a preference for laser treatment:

> *All I said, I know is the young oldish man by me had it done with the laser beam see. So I said I'd like it done with the laser beam. So when I went down again I seen Mr W____ and he said 'you wanted it done with the laser beam didn't you' and I said yes. Well he said you can count that out. He said if I do you with a laser beam he said it would damage your kidneys and he said you will have a bag (catheter) all your life. That's what he said, so he said 'what we've got to do is we got to take the tissue out and that's what they done. [Mr Allgood: a dislike of randomisation]*

Interestingly, one non-participant sees his treatment allocation as a form of rationing (a rationalisation among participants):

> *Well it didn't come to the point where I needed a choice. They seemed to say that your condition is not so bad as to need surgery, therefore we recommend you have tablets and that's really how it was presented to me. [...] and of course would be a lot cheaper over the period of time, although it would take longer to effect, I was quite happy with that. [Mr Frame: no reason given]*

Two (Mr Flynn and Mr Frame) indicated that they were willing to participate in future trials.

> *It rests with them, I'm willing to do whatever they want to do, and if they said come in and we'll do it then I'll do it. [Mr Flynn: treatment preference]*

One (Mr Flynn) would agree to whatever the clinician suggests:

> *Well I don't mind what they say, you know, wait till what they dec..suggest, go from there. Not really looking forward to operation if they can clear it up with medication. [Mr Flynn: treatment preference]*

Similarly, Mr Frame has no recall of being asked to participate. However, his career as an engineer meant that he had a clear understanding of experimentation. He believes he would agree to participate if asked:

> *I don't remember being asked at all [to take part in the trial]. Now he may have said these things but I certainly don't remember. The reason I would have responded in the way that I would have agreed for trials was because all my life at British Aerospace I was*

involved with engineering which involved a great deal of testing and I know the benefits of going through stringent testing and weighing this method against that method, length of times, temperatures and all sorts of things like that so had he asked me I would have approved. [Mr Frame: no reason given]

Acceptance

As previously indicated there appeared to be three pathways to refusal: those who made an active decision not to take part, those who believed that they had agreed to participate and those who had no recall of being invited to participate.

The majority seemed to have a good or at least a partial recall of being asked to participate in an experiment, with some also able to recall aspects of trial design and methods. However, as with the participants, many of these patients also believed variously that they had been directed towards a treatment by the recruiting clinician (individualised treatment) and that the treatments were being rationed.

Such beliefs were also associated with trust and distrust and this is similar to the experience of the participants. A number of these patients expressed anxiety about their condition and their treatment and this may be one reason they became non-participants.

Table 21: Acceptance

Non-participant	Trust	Distrust	Anxiety	Altruism/ personal benefits
Mr Becker	✓			
Mr Ladbroke			✓	
Mr Maynard	✓			
Mr McCarthy	✓	✓	✓	✓
Mr Young	✓	✓		
Mr Frame	✓			✓
Mr Frost		✓	✓	
Mr Gibbon	✓	✓	✓	
Mr Williams			✓	
Mr Allgood	✓			
Mr Flynn		✓	✓	

Trust

As with the participants, a number of these men (Mr Allgood, Mr Frame, Mr McCarthy, Mr Maynard and Mr Young) felt that as laymen, they did not have the expertise or experience to make such decisions about their treatment and were dependent upon the clinician to guide them.

> *What did you think about the information they gave you about the different treatments?*
>
> *Well what he told me? Well I could only go with what he said you see what I mean. I couldn't go against him because I told him I says I don't know nothing about it I said you're the person I said I don't know nothing about it. But they treated me all right and it is a wonderful ward yeah it is I like it yeah it was a wonderful ward they're really good. [Mr Allgood: a dislike of randomisation]*
>
> *So the last couple of times you've been to see the consultant did he ever mention a laser treatment?*
>
> *Yes, well I'm not a medically trained person so I can't comment on it but I've read about it in the newspaper about two or three years ago and they were doing some trials in S_____ using it. [Mr McCarthy: treatment preference]*

Such trust was also typically expressed as a belief in the clinicians as experts:

> *They are the experts not me. I mean all I know is the problems I've got. My problems seem to be the same sort of problems that everybody else has had before they had their operations. So ... you know all I can say is that I've got problems of prostate trouble and it seems to be quite common with everyone I've spoken to and everybody I've spoken to said in the end they are OK. Which is what I hoped I would've been OK. [Mr Maynard: treatment preference]*
>
> *Did you have any expectations when you were referred about what they could do for you?*
>
> *Well the image I've got in my mind is that when you go to your GP and he says yes you've got this, that, oh I'll refer you to the experts, that's what I would say you know. So down to the hospital you go and they examine you and it's over to them you know, the GP doesn't seen, not that he's not interested, he just*

gets feedback I suppose oh yeah, you're cured or you're not cured you know. [Mr McCarthy: treatment preference]

Would you've been happy to leave it to them?

Yes I think so, yes cos I think with treatments of any sort I mean you don't know enough about it yourself. You've got to trust the professionals haven't you, it's like getting the plumber in (laughs) you know. I mean you trust him to do the job properly and that's that. Quite happy normally. [Mr Young: travel]

They sometimes appeared to be willing to accept whatever the clinician suggested. They trusted the clinician to direct them to the 'best' treatment:

Well what I should do is went where the doctor told me, yes, if he said laser beam I should have it done with a laser beam but I think they would've known. Yeah, yeah, the man I spoke to they would've known, yeah, yeah. He told me out straight, he said 'you cannot have it done'. Well I said this gentleman's all right he's living in the flats over there he said 'you cannot have it done'. [Mr Allgood: a dislike of randomisation]

This acceptance was extended to participation in the trial itself in some cases:

How about the fact that by doing the trial the doctors are saying we don't know which is the best treatment?

I'm not sure what to say about that.....Well I wouldn't be worried about that because I would recognise immediately that if there was something they were uncertain about the fact they were carrying out that test, first of all they would recognise that it wasn't dangerous and I would recognise that the results would be such that it would go some way to satisfying their uncertainty in the future. [Mr Frame: no reason given]

For Mr McCarthy, his willingness to accept the trial was linked to the rapport and thus the trust he has in the recruiting clinician.

As long as they don't treat you as a sort of, like a, didn't have the attitude that you're just a patient and you're, you don't sort of have any rapport from it. In other words they're not telling you what they're doing or anything about it if you are interested. I mean a lot of people probably are not interested you know, but I would be you know. [Mr McCarthy: treatment preference]

However, Mr Gibbon believes that he has no choice but to trust the clinician:

How do you feel about that?

Well there's not a lot I can do about it is there? You know I'd rather they'd said there the actual doctor approved because well that's why you're going in, isn't it. You know I don't want to go through this thing and then say ah well I'm sorry but you're back to square one. What happens then? [Mr Gibbon: treatment preference]

Distrust

A few non-participants were distrustful of some aspects of their experience. There was a general suspicion (Mr Flynn, Mr McCarthy, Mr Young, Mr Frost and Mr Gibbon) that the clinicians were holding back some information about the trial or their treatment:

What happened?

Well they won't tell you will they. [Mr Flynn: treatment preference]

How did you feel about that?

I don't know, I don't really know because they said oh no it won't be drugs and I thought well if it isn't enlarged, why won't it be drugs, this is the way my mind was working you see. If it was enlarged, they'll say oh we'll have to cut it, but if it isn't, why not drugs. Because if it's not enlarged, why are they cutting it? Obviously there must be something but they haven't told me, not in as many words. [Mr Gibbon: treatment preference]

When he said that he wouldn't try to persuade you one way or another do you think he was ...

I don't think he seemed to be offering any advice at all, probably thought he couldn't you know you have to be very careful these days. You know they are in a very difficult position I think these doctors these days, very difficult. I mean everybody's suing everybody now aren't they (laughs), you know they've got to be a little careful I suppose. [Mr Young: travel]

This is associated with the belief that the clinicians are rationing treatments (Mr Maynard, Mr Becker and Mr Frame). For example, when Mr Maynard did not receive treatment, he became cynical about the trial, believing he had been excluded:

If you had taken part in the trial you would've had an equal chance of getting the operation, laser or waiting.

> *What I still find confusing is if it's not so serious as he thought and therefore they weren't going to do the trial, how come he offers the operation? It seems a bit well strange to me. I would've thought if it wasn't serious enough to go into the trial, how come it's serious enough to offer me an operation? It's not very consistent is it? So I'm a little bit up in the air about it. I'm not entirely satisfied that everything has gone as it should've done but somehow or other it's come off the line somewhere so I'm not terribly happy about it. But if there is to be something done eventually then you I am quite happy with whatever is on offer it's as simple as that really. [Mr Maynard: treatment preference]*

Looking back, Mr Gibbon believed he might have gained quicker access to treatment:

> *Having said that, I wonder if it has, because the bottom line in my mind is that had I said yes I might of had this done now you know. So that did cross my mind to be honest. I thought well if I'd said yes, oh yes I'll go on this laser thing, would they have said right come on it we'll do it. Rather than say well, you refused the laser you're on the list. So that did cross my mind if I'm honest, yes and I don't know if that is the case or not. [Mr Gibbon: treatment preference]*

This is similar to the way some participants made sense of their treatment allocation (see previous chapter).

Anxiety

For half of these patients (Mr McCarthy, Mr Frost, Mr Ladbroke, Mr Williams, Mr Flynn and Mr Gibbon), the decision to participate or not in the trial was not their only concern. Four (Mr McCarthy, Mr Ladbroke, Mr Frost and Mr Williams) were apprehensive about having surgery and what that involved and two were concerned that their symptoms may indicate cancer (Mr Flynn and Mr Gibbon). These are sensible reasons for not wanting to be involved in the trial and may be why they are 'refusers'.

> *I've had excellent treatment and everything else but it's me, I'm a coward. Why I asked about this laser treatment is because within the laser treatment procedure they said that they use a general anaesthetic and that's one of my biggest fears. I just, that's a big barrier for me you know so I must admit I'm a coward you know that's that. I can go to the dentist, I can do anything else you*

know most other things anyway but it's just that's the big barrier. [Mr McCarthy: treatment preference]

So what did you think it would be?

Not really, I was more terrified of what it would it be. You know you hear all these ....

Were you worried about cancer?

Naturally, yes and he said no the prostate isn't enlarged that he could discover but I will send for you again and you'll come and have various tests and flow tests that and then I was referred to this [clinic]. [Mr Gibbon: treatment preference]

Case studies

As for the participants, each individual non-participant's narrative was also analysed as a case study. This helped to elucidate the different pathways to non-participation.

The two examples described below have been chosen because they show a number of the different ways in which these men struggled to make sense of their recall of the trial and their experience of non-participation. Mr Gibbon is an example of a clear non-participant and in contrast, Mr Frame is a non-participant who believes that he would have agreed to take part if approached.

Similar levels of knowledge of experimentation appear to produce different yet internally consistent accounts of being asked to participate. Their rationalisation of non-participation also appears to be similar to those of participants.

Mr Gibbon

According to the trial records Mr Gibbon, a 62-year-old former coach driver (he took early retirement) was eligible to participate in the trial but made the decision not to participate. He confirms that he made an active decision not to take part in the trial. The information he had about randomisation proves problematic; he does not comprehend why they cannot tell him which treatment he will receive. There was an element of suspicion within this account:

What did you think of the idea of being randomised.....?

> *Er, I hadn't really thought about it but yeah, it seemed a bit vague that. If they want to have you, if they say will you take part in this I think well they should say well yes you are going to do it rather than saying oh yes I'll take part and them saying no we don't want you. I think if you said yes, you are willing to take part in this, then they should do. [Mr Gibbon: treatment preference]*

This leads him to reject the trial in favour of the standard treatment, which he believes to be the most effective treatment:

> *Well I think me being me, if the TURP's is the standard one then I'm quite happy thank you because that's been proven with everyone else. Having said that I appreciate someone's got to do, you've got to have someone for research and all that. But me worrying, no thank you, I'll stick with the one that's tried and tested if it's all the same you know. That is my way. [Mr Gibbon: treatment preference]*

He appears to be influenced by the recruiting clinician, who, after introducing the option of trial participation, also offers the alternative of the standard treatment:

> *She said I don't really think this is in your best interests, I think you are far better off sticking with the normal treatment and I said yeah, I think you could well be right. [Mr Gibbon: treatment preference*

This patient stated that he would have agreed to whatever treatment option the clinician directed him towards:

> *No because I more or less went by guidance from [the recruiting clinician], [he] said about this and I said yes that sounds lovely and as they explained it on [date] it was [the recruiting clinician] that noticed more or less the change in me. [Mr Gibbon: treatment preference]*

There are a number of possible interpretations of this exchange. The clinician may have intervened as a sensitive response to the patient's anxiety, attempting to make it easier for him to say no. Alternatively, this may be an example of the clinician actively directing a patient away from the trial because he/she believed in was not in his best interests or that the standard treatment was the most suitable for his particular symptoms/condition.

It is interesting to consider the outcome if this patient had been recruited by a different clinician who might not have had such an awareness of this patient's anxiety and so continued with the process of recruiting him onto the trial.

Mr Frame

Mr Frame, a 69-year-old former aeronautical engineer, was able to recall experimentation, in that he knew about clinical uncertainty and the comparison of treatments. Yet he had no recall of being asked to participate in this specific trial. Given this amount of knowledge, one might expect him to recollect being asked to take part in this specific trial.

> *Now he may have said these things but I certainly don't remember. [Mr Frame: no reason given]*

He believed he was directed by the clinician, who informed him that treatment was not necessary:

> *As a result of that flow test I met the consultant, that was on [date] of this year and he told me the flow test was such that it wasn't too bad. I was middle of the way, I can't remember what he described as the middle of what, at the borderline for tablet treatment and wasn't really necessary for me to have surgery. Now I went on from there and I've got another appointment there on [date] of next year to find out how the tablets are working. [Mr Frame: no reason given]*

Yet he was willing to accept whatever the clinician suggested, including trial participation. He had trust in the recruiting clinician who appeared to treat him with drug treatment:

> *The consultant at the last occasion when I saw him on [date] he did say that sometimes the surgery wasn't always as successful as has hoped it would be so the tablet form in my case was probably just as well to do that and er I accepted his word for it. [Mr Frame: no reason given]*

He believes he would have agreed to participate if approached. Based on his career as an engineer, he acknowledges the importance of experimentation and the testing and comparison of treatments:

> *I would've agreed to say I'm perfectly happy to take part with any form of randomised treatment. But whether it was going to be a trial test or whether it was to be the final test I wasn't aware in*

> *the slightest because of the nature of my previous work I recognise the necessity of carrying out tests for the benefit of anybody and everybody concerned so I just would have agreed. [Mr Frame: no reason given]*

He accepted the option provided by the recruiting clinician:

> *They didn't leave me with a choice. In fact I recognise that they were saying that your condition was not as bad as many people that we've met. [Mr Frame: no reason given]*

The trial records indicate only that he 'refused'. It is surprising that this patient has no knowledge of the trial when he has such a clear understanding of experimentation and has such a strong belief in the importance of experimentation. Although it may be that this patient has forgotten being asked to participate, he does appear to be strongly altruistic. Although there is no other information available on the clinician's experience of this consultation, one possible explanation is that the clinician may have directed the patient to a treatment or did not actually attempt to recruit this patient onto the trial.

Conclusion

Thus the majority of these non-participants appeared to have at least a partial recall of being asked to participate in an experiment, with some also able to recall aspects of trial design and methods. However, their recall was at a lower level than that of the participants. There appeared to be three pathways to refusal, those who made an active decision not to take part, those who believed that they had agreed to participate or had no recall of being invited to participate. Trust and distrust were strongly associated with how these men made sense of their treatment allocation and of being asked to participate. A number also expressed anxiety about their condition and their treatment and this may be one reason they became non-participants. There are, therefore, some clear similarities but also some specific differences between participants and refusers. These issues are considered further in the next chapter.

Discussion

Within this chapter, I will discuss the empirical findings contained within chapters 5 and 6 and examine participants' and non-participants' struggles to understand their participation in the RCT. These findings will also be examined within the context of their implications for trialists and within the current ethical and methodological debates and the literature examining trial participation.

Introduction

Historically, the literature examining the RCT has emphasised the ethical and methodological issues that should be taken into account in the design and implementation of an RCT. Debate about the ethics involved in the RCT (see chapter 1) have examined issues of equipoise; the appropriateness of randomisation, blinding and placebos; and the dilemma of which groups should be included or excluded from trials. Attention has often focussed on the importance of the informed consent procedure. These debates have influenced the design of the RCT, although these developments have been primarily from the perspective of trialists, hence there is little consideration of the perspective of participation in RCTs.[35]

Textbooks and reports in journals focus on the design, methods and results of trials,[15, 106, 176] suggesting that each decision in the planning and design of a trial, from selecting the intervention, the population, and the aims of the trial, occurs in isolation and according to standard rules. However, there is an increasing awareness of the problems of attaining the required level of precision, validity, and the feasibility of this approach (see chapter 2). Such decisions may influence the behavioural dynamics of participation and affect the internal and external validity of a trial.[129] Thus the role of the trial participant has predominantly been viewed as a source of data and as a potential source of bias, with the possible impact of these design issues on patients often ignored.

However, studies examining the public's and patients' perspectives of being involved in RCTs have primarily been undertaken from the perspective of

trialists, often using hypothetical trial scenarios with a variety of lay or potential trial populations with the ultimate aim of improving accrual within future trials. The reliance of such studies on hypothetical vignettes is problematic and possibly misleading; those who have taken part in a trial may have a real and distinct difference of opinion compared to those whose responses are based on speculation.[178, 182] Studies that explore the experience of actual participation have predominantly used structured questionnaires to examine motivation, satisfaction and barriers to recruitment. Their focus on informed consent, often evaluating effectiveness using recall and recruitment rates as opposed to patients' views has also tended to reflect the perspective of trialists. Only recently and in a few studies[42, 173] has there been an assessment of the perspective of actual participants: their attitudes towards, their experience of, and motivation for, taking part in a clinical trial.

Hence this study carried out in-depth interviews with participants and non-participants in an actual randomised controlled trial comparing surgical and conservative treatments for a common disorder in older men: lower urinary tract symptoms related to benign prostatic disease.

In the previous two chapters, participants' (22) and non-participants' (11) recall and understanding of what the ClasP trial involved were examined. It was found that the majority of the participants were aware of some aspects of randomisation and most (15/22) acknowledged the involvement of chance in their allocation. As with the participants, a large number of the non-participants were also aware of some aspects of randomisation. Almost all (9) could recall that the trial was some sort of experiment. However, only a small number (4/11) were aware of the involvement of chance.

All but one (Mr Taylor) of the trial participants incorporated multiple accounts of how they might have been allocated to their treatment. As previously indicated, many had a good or at least a partial recall of the major aspects of trial design and methods. However, the majority also held other co-existing ideas about non-randomised methods of allocation such as rationing and individualised

treatment, which they used to understand and explain their treatment allocation. For a small number, altruism (7) and an expectation of personal benefits (7) were motivations for taking part. However, trust (10), distrust (11) and beliefs about fate and destiny (13) were evident as they tried to make sense of their treatment allocation in relation to their treatment preferences. The interview data and particularly the case studies illustrate the struggle that the participants engaged in to help them understand the experience of participation.

The majority of the non-participants appeared to have at least a partial recall of being asked to participate in an experiment, with some also able to recall aspects of trial design and methods. However, their recall was at a lower level than that of the participants. Three main types of refusal were identified: those who made an active decision not to take part in the trial (5), those who believed that they had agreed to participate (3), and those having no recall of being invited to participate in the trial (3). Surprisingly a small number of non-participants also appeared willing to participate in the trial, citing trust (7), personal benefits (4) and altruism (2) as motivations to take part.

Among those who made an active decision not to take part, wanting individualised treatment and having a treatment preference both appear to be important motivations. A dislike of the trial design and randomisation were also important among this group. Those who believed that they had agreed to participate or had no recall of being invited to participate all believed that they had been directed towards a treatment by the recruiting clinician. They appeared willing to accept whatever treatment the clinician suggested and sometimes believed that the clinician had guided them towards a particular treatment. Non-participation for some was associated with their lay beliefs about what trial participation involved and was seemingly unintentional. However, a number of these men (6/11) expressed anxiety about their condition and their treatment and this may be one reason they did not take part in the trial.

The participants and non-participants appeared to be very similar in terms of how they made sense of the trial. Only around half of the non-participants

actively opted out of the trial, and as with the participants, this group produced multiple accounts of how they had been allocated to their treatment. Trust and distrust were strongly associated with how these patients made sense of their treatment allocation and of being asked to participate. Thus there are some clear similarities but some specific differences between participants and refusers and these issues are considered further within this chapter.

A large amount of information was also gathered about these patients' symptoms, outcome, and knowledge of the treatments available within the trial. However, this chapter will focus particularly on RCT participation, using this material as context where appropriate.

Reasons for willingness to participate

The personal motivations for trial participation, both hypothetical[49, 58, 99, 124, 143-148, 150, 177-186] and actual,[68, 83, 97, 105, 181, 187-199, 201] have been well documented within the literature. These have been reported to be altruism, an expectation of receiving personal benefits from taking part in the trial and trusting the recruiting clinicians.

Altruism

In examining the reasons why these patients were willing to participate it is clear that a small number had altruistic reasons for participation: to help clinicians to improve their clinical skills and to contribute to medical progress. Surprisingly, two non-participants also stated that they would agree to participate for altruistic reasons:

> *I recognise the necessity of carrying out tests for the benefit of anybody and everybody concerned so I just would have agreed. [Mr Frame: no reason given]*

Within the literature, there are no studies that reported the altruistic desire to help clinicians to improve their clinical skills. The hypothetical studies and those

examining trial participants have found that altruism was mainly expressed as a desire to help 'others' and future patients.[49, 58, 97, 105, 124, 146, 148, 150, 177, 179, 181, 183, 190, 192, 196, 201-203] The progress of science was also an important motivation within the studies examining participants.[68, 83, 97, 148, 150, 177, 179, 181, 183, 189] However, many of these studies examined Phase 1 trials where such high levels of altruism may be associated with both the nature of the trials and the seriousness of their condition.

The desire to help future patients and to contribute to medical progress was mentioned by fewer than expected within this study given its prevalence within the literature where altruism is commonly found to be a motivation ranging from 26% to all participants within a trial. However the role of altruism as a motivation to participate is variable and a small number of studies have also questioned its importance.[143, 178, 188, 191]

Such differing levels of altruism may be associated with the different methodologies employed by these studies. Surveys and structured schedules used to examine both actual and hypothetical participation found high levels of altruism ranging from over half (56%) up to 100%. Hypothetical studies using qualitative methods also found high levels of altruism. However, such motivations are perhaps to be expected from predominantly lay groups where responses are based on speculation. In contrast, altruism was a weak motivation within the small number of studies examining actual participation using qualitative methodologies to examine the experience of participation.[83, 193, 196, 201]

Personal benefits

A similar number of these men had an expectation of personal benefits such as obtaining faster and possibly superior treatment within the trial. Participants (7) often thought that taking part must have an advantage of obtaining quicker treatment:

> *Again to be perfectly honest, I chose, I was quite happy to go the clinic way and at the same time at the back of my mind was, well*

> *if I go that way I might get treated quicker than if I go the other way. [Mr Taylor: allocated to and preference for TURP]*

Within the literature, obtaining the best care has been reported to be an important motivation for some patient groups.[49] However, such benefits within many trials were often unrealistically high, especially within Phase I trials where the actual chances of receiving any personal medical benefits from such trials was small.

Among the non-participants here, four focussed on the belief that they had been excluded from receiving the 'new' and more advanced treatment, and with the idea that the function of the trial was to ration this treatment. Within this particular trial, this belief often appeared to be triggered by the recruiting clinicians, who informed the men that the laser treatment was only available within this trial. These patients believed that this new treatment had been incorporated into the trial by the recruiting clinicians as an inducement or 'carrot' to take part:

> *He read the back page [of the questionnaire] and then he closed it again, put it down and said 'well what about a laser' and I said 'yes fine' and he said to me 'I'll just check' and out he went and came back in and said no to the laser. It was like a carrot like 'here it is but we can't give it to you now' and then out of the blue I thought then he was going to say well nothing just stay on the tablets well then he said to me 'what about an operation' and I thought well OK. [Mr Maynard: treatment preference]*

A few participants similarly found their allocation to conservative management difficult to accept. Despite being able to recall the involvement of chance in their allocation, these participants also wanted and expected 'treatment'. This was often interpreted as their exclusion from treatment and this was often upsetting for these patients.

> *I never got any chance of getting laser. Cos I says to her, can I have the laser [Mr Symonds: allocated to CM and preferred treatment]*

Thus the hope of obtaining the 'new' or 'experimental' treatment was an important motivation for many of these participants and non-participants.

Within the literature, this has also been cited by many willing, hypothetically, to participate as their main motivation.[143, 145, 148, 179, 183] For example, 72% of UK oncology patients welcomed the 'greater chance of receiving *new* treatments', although many (27%) also indicated that the least appealing aspect of participation was the 'chance of obtaining *experimental* treatments'.[150] Similarly, a small number of the non-participants within this study also cited a dislike of the trial design and randomisation within their rationale for not taking part in the trial.

Trust

A number of previous studies have indicated that trust in the clinician often constitutes an integral part of participants' decision making,[190, 191, 193, 194, 196] with a large number believing that their clinician always acted in their best interest.[97, 188, 189, 198, 201] Trust in their clinician or clinicians generally was an important factor for many who were willing (hypothetically) to participate.[143, 148, 178, 179, 182, 183] The literature also indicates that the perceived expertise of the recruiting clinicians may also play an important role in recruitment.[150, 177, 178, 182] However this finding was principally within trials of patients who had a life threatening condition.[150, 190, 191, 193, 194, 196, 198, 201]

Trust was also important within the accounts within this study. Trusting the clinician involved in the men's treatment as well as trust in medicine was evident within many of the accounts of both participants (10) and non-participants (7). Typically, among both these groups, this trust was expressed in terms of the doctor being an expert and among participants this extended to doctors the wider medical profession. This trust also included trial participation itself among participants and surprisingly also among some non-participants. A small number of these participants and non-participants felt that, as laymen, they did not have the expertise or experience to make such decisions about their treatment and were dependant upon the clinician to guide them.

An association between socio-economic status and willingness to trust the recruiting clinician has been identified. A large scale survey of a UK lay population found that those who were older (60-70years) and from lower socio-economic groups were more (hypothetically) likely to agree.[178] However, this was not reflected within this study. The majority of the men within this trial were categorised as 'working class' and four (Mr Bowler, Mr Murray, Mr Grange and Mr Bullock) as 'middle class'. The four 'middle class' men had varying levels of recall and understanding of the trial and randomisation and the majority (3) appeared equally to incorporate trust into their accounts of participation as the 'working class' men. For example, although Mr Murray (a teacher) had the highest level of knowledge about randomisation and the trial, he also used fate, destiny and trust to make sense of the trial. The two 'middle class' men who were non-participants in this study had varying levels of recall. Although one of these men had made an active decision not to take part (Mr Ladbroke), Mr Frame (a former aeronautical engineer) had a clear understanding of experimentation and randomisation and expressed a strong willingness to participate, but had no recall of being asked to participate in this specific trial.

Thus, although on one level trust was an important motivation to participate, it was also an important element within the men's struggle to make sense of the trial and participation. This will be discussed in more detail below.

Non-participation

Few studies have examined non-participation. Those that have examined why people refuse to take part in clinical trials are primarily set within the context of how to improve the response rate for future studies. The main focus has been an examination of non-participation within trials that present trialists with specific accrual or ethical problems such as HIV[144-147, 183-185] and oncology.[49, 142, 150, 186]

Among the non-participants here there appeared to be three pathways to refusal: those who made an active decision not to take part, those who believed that they had agreed to participate and those who had no recall of the trial.

Within the literature there is often an expectation that trial design issues such as randomisation, experimentation and research methods would be an important rationale for refusal. However, only a small number of participants within a few studies actually cited such reasons.[50, 126, 148, 209, 210] Trial design was problematic for a number of those asked to participate in hypothetical HIV vaccine trials. However, the aim of these studies was to assess the acceptability of the design of such trials. Similarly, a study specifically examining patients' and clinicians' views of trial design found that randomisation (39%) was the main reason for non-participation among breast cancer clinicians and their patients (58%).[49]

Among the men who made an active decision not to participate in this study (5), all cited some aspect of the trial design and randomisation. The decision not to participate was sometimes made because these men received no direction from the clinician as to whether they should participate in the trial or not:

> *I said what do you think is best, well he said well, I won't advise you he said, it's up to you. Well I said I'll have the operation and I went and had the operation and that was very good. [Mr Young: travel]*

All five of these 'true refusers' also expressed a treatment preference, with the majority wanting TURP because they believed it to be the standard and most effective treatment. These men wanted the 'right' treatment. This was based on their inability to accept clinical equipoise and the belief that the standard treatment would be more effective:

> *I mean in all forms, if it's going to be surgery, all right surgery has got to be positive, there's no point to my way of thinking to having some surgery if the problem isn't eradicated. [Mr Frost: dislike of randomisation and research]*

Half of the non-participants (6) expressed anxiety about their treatment and were apprehensive about having surgery and what that involved. Two were concerned that their symptoms may indicate cancer. These are sensible reasons for not wanting to be involved in the trial and may be why they are 'refusers'. Concerns about safety were also prevalent among those asked hypothetically to participate in a range of trials.[148, 180, 181] One non-participant based his decision to

refuse on a (valid) assumption that the trial would be more time consuming than the standard treatment. Logistical problems such as transportation and inconvenience were also mentioned by a small number of patients as reasons for non-participation in other published trials.[97, 126, 181, 209, 210]

A distrust of modern medicine (52%) and the hospital (19%) was cited by non-participants in a small number of studies.[50, 58, 97, 141] However, the issue of mistrust, mainly arose amongst those who would refuse to participate in HIV vaccine trials.[145-147, 183, 184] Such beliefs were also associated with trust and distrust and this is similar to the experience of the participants here and will be discussed in more detail below.

This rationalisation of the trial appears to be similar to those of participants. It is interesting to speculate how these non-participants, who are in many ways very similar to the participants, came to be non-participants. The interaction between the clinician and the patient does appear to influence the direction these men take to participate or not in the trial. This will be discussed in more detail below.

Recall and comprehension of the trial

Within the literature, the majority of studies have focussed on patient recall rather than comprehension, often based on participants' own rating of their understanding of the trial (see chapter 3). Participation rates, both hypothetical and actual have also been used to indicate the effectiveness of the informed consent procedure. A smaller number of studies have used the informed consent procedure or international guidelines to evaluate participants' understanding. These studies appear to be attempting to examine understanding against some objective criteria, however, such criteria are not defined by these studies and are predominantly used to inform the questionnaire design. These studies still fail to unpack the meaning of trial concepts, although a number do demonstrate that patient recall does not reflect understanding.[101, 103, 105, 217]

Only a small number of studies have examined trial participants' understanding of what a trial involves and have asked them to describe the trial in their own

terms.[42, 173, 200] However, the majority of these studies fail to examine participants' recall or to define how participants, clinicians and researchers understand these trial concepts. The main criticism of such studies is that they "only give a weak clue as to what patients had understood of the questions and hence what they meant by their responses" (p.1210).[72]

Randomisation is a complex concept and this study considered recall and understanding as six integral elements: the involvement of chance in their allocation, that envelopes were to be used to allocate treatments, that the treatment allocation was concealed, that treatments were being compared, that clinicians were uncertain about the most effective treatment, and that they were participating in an experiment. These aspects were included in the trial patient information leaflet (see Appendix 1).

As chapter 5 showed, most participants were able to describe some aspects of the concept of randomisation, particularly in terms of the involvement of chance:

> *Well I'm prepared to go in and take my chance. [Mr Hall: allocated to CM, no preference].*

> *Well it's a bit like the lottery isn't it really, I'm not very happy. [Mr McCarthy: treatment preference]*

Some had a more detailed understanding of treatment comparison, concealed allocation and experimental design. In chapter 6, it was shown that levels of recall and understanding were lower for non-participants, with only a small number (4) having an awareness of the involvement of chance. The majority of those who, according to the trial records were eligible but decided not to participate, were able to describe the experimental nature of the trial:

> *Well I suppose my initial reaction to that is that I might be at risk a little bit in being a guinea pig. [Mr Ladbroke: a dislike of randomisation]*

If this study had utilised a structured questionnaire to assess knowledge of the trial, the majority of these participants and non-participants would probably

have been shown to understand the concept of randomisation in basic terms and would have indicated an awareness that they were taking part (or had been approached to participate) in a trial. The use of qualitative research methods, however, showed that these participants and non-participants also held a number of other apparently contradictory beliefs about the treatment they received. They believed variously that the treatments were being rationed and that their therapy should have been individualised. Such beliefs were associated with trust and distrust in their clinicians. Over half (13) of the participants additionally believed that fate and destiny were also involved in their allocation to a treatment.

The struggle to understand

The previous two chapters have assessed patients' recall of the trial and beyond that, an investigation of their understanding of the underlying concepts. The key to understanding peoples' experiences of RCTs lies in the basic inconsistencies of trial design, as shown in these men's struggle to piece together what participation means. Each individual's narrative about trial participation was analysed as a case study and this showed that most engaged in a dialogue to try and make sense of the trial design, using their lay beliefs and their actual experiences of the trial and to construct an explanation.

Participants adopted several approaches to making sense of the trial. Some cynically interpreted this as rationing and had a distrust of the clinicians (see Mr Pierce); others put their trust in their clinician and their beliefs about fate and destiny (see Mr Watson), while others just keep struggling with the perceived inconsistencies (see Mr Symonds).

Surprisingly, the non-participants made sense of their experience of being asked to participate in similar ways. Some placed their trust in the clinician, believing they received the best treatment by individualised care (see Mr Young). For others, the best treatment was thought to be within the trial and thus they believed that they had been excluded from the trial and that the most effective treatment was being rationed and denied them (see Mr McCarthy).

Many patients could recall the trial and randomisation, but the trial did not easily make sense to them in their own terms. Such a method of treatment allocation seems too haphazard and does not appear to be based on clinical evidence.

Thus, in attempting to make sense of their participation (or not) in this trial, these men produced narratives which on the one hand described their understanding of elements of randomisation, but on the other hand challenged these understandings with, for example, the desire to trust the clinicians to make treatment allocations based on individual clinical characteristics. Both the participants and non-participants made sense of their experience using these similar rationalisations. For example, participants sometimes believed that randomisation was being used to ration limited resources (5), and some non-participants (5) similarly believed that they had been excluded from the trial and thus denied access to a treatment they might have preferred.

Many participants characterised their struggle to understand participation by their questioning of this method of allocating them to a treatment. They recalled the mechanics (chance, the use of envelopes etc) but not the theoretical rationale for its use. For example, Mr Symonds searching for an explanation for why there were three treatments, found it hard to believe that they were equivalent:

> *Do you think they had a preference. Do you think they thought one treatment was better than another?*
>
> *I think they do, obviously they must, I mean, what would they have three treatments for? You know they don't tell you why they've got the three treatments, especially ..... they didn't say we're going to do this one for that if you're this way inclined or that one for that way inclined or the other one because you've got to take the, you know the other one. You know they didn't give you any reasons why there's three. If they gave you reasons you'd be able to choose. [Mr Symonds: allocated to CM and preferred active treatment]*

Mr Hall also had a good recall of the trial and randomisation in terms of chance, comparison, concealed allocation and the use of envelopes. However, although

he knew that envelopes were used to allocate him to a treatment, he was none the less confused as to *why* this method was being employed.

> *So it's shared out more or less, whichever envelope they open then. so why don' t they say which one they want really to suit them. Why don't they say we'd like you to do this, we'd like you to do that, or we'd like you to have the operation. Why don't they just tell me straight, why allocate it? [Mr Hall: allocated to CM, no preference]*

The existence of such different accounts about treatment allocation could be indicative of confusion or distortion, as suggested elsewhere.[42, 67, 173] The men in this trial acknowledged that randomisation was confusing (see Mr Webster and Mr Maynard above). Closer examination, however, suggests that these apparently contradictory accounts are consistent in their own terms. For example, the number and complexity of tests and questionnaires participants completed during the trial reinforced the men's view that treatment should be determined by clinical and personal characteristics (symptoms/age). In contrast, some non-participants believed that the initial questionnaires they were asked to fill out confirmed that they were actually participating in the trial.

Similar recall of the trial and experiences of participation can produce different yet internally consistent accounts of participation. For example, this can lead to a belief that treatment should be individualised (Mr Watson) or that the clinicians were rationing treatments (Mr Symonds). Any confusion that arises comes from their attempts to make sense of their experience by trying to piece together apparently contradictory accounts - not confusion relating to a lack of understanding of randomisation *per se*.

The patient perspective: implications for trial design

While the incorporation of multiple accounts could indicate that these men were confused about randomisation,[42, 173] an alternative explanation would suggest that their views are internally consistent and a reasonable reaction to a difficult situation: participating (or not) in an RCT. The practicalities of being in the trial, the role of the clinician and how these men incorporate these events into their

accounts all appeared to contribute to this. These findings have implications for trial design and for trialists as such beliefs may affect the internal and external validity of a trial.

Trial terminology, treatment preferences, the role of the clinician and the impact of the practicalities of the trial design can all influence participants in terms of both their willingness to participate and their beliefs about how they had been allocated to the treatment they received.

The participants' understanding of trial terminology, treatment preferences and their trust and distrust in the recruiting clinician all appeared to influence their interpretation of what the trial involved and its implications for them.

Lay understanding of trial terminology

The terminology used in trials can have different meanings to participants and trialists. As Altman points out, randomisation does not mean that allocation is "haphazard"(p.86), but that patients have an equal (or known) chance of being allocated to any of the trial interventions.[18] In contrast, the lay definition of randomisation is of a 'random event' with no purpose to it and thus participants unsurprisingly believed randomisation to be an indiscriminate, haphazard and unplanned method of allocating them to a treatment.

These participants and non-participants also held various other interpretations. For example, the use of lay interpretations of randomisation such as 'luck' (Mr Hall) and 'lottery' (Mr McCarthy) implies that they believe that there is a winner who receives the 'best' treatment. For those who took part in the trial, their actual allocation was also believed to be due to fate and destiny and for some was 'pre-ordained' (Mr Grange). Hope was also present within these accounts: *'So it's something that you just have to hope goes well'* (Mr Stone). Such beliefs were linked to a failure to understand clinical equipoise, the belief that one of the treatments is more effective: *'I just hope I pick the right one'* (Mr Daw).

Many patients had difficulty resolving the apparent differences between their lay understanding of randomisation and their beliefs about how they would want to be allocated to a treatment. Such lay perceptions of 'random' frequently interfered with participants' understanding or acceptance that this was how they had been allocated to their treatment. For example, although Mr Webster acknowledges that chance is involved in his allocation, this does not reduce his difficulty accepting such an occurrence. He interprets randomisation to be an indiscriminate method for deciding which treatment to give him:

> *What did you think about being randomised?*
>
> *Well that was a bit confusing, it was like they know what's wrong with us. I thought it would be just one operation and that was it. If it was an operation, if they could have cured it by medication they would have decided there and then, the other consultant would've decided. You know this lad need medication, or yes this lad needs the operation. [Mr Webster: allocated to TURP, preferred laser]*

Randomisation is perceived to lack the direction or purpose expected from clinicians and he acknowledges that he finds it hard to accept that treatment would not be allocated in response to his symptoms:

> *I could understand it but I couldn't realise, cope with the idea that whatever the symptoms were that was the envelope we were going to get. [Mr Webster: allocated to TURP, preferred laser]*

Similarly, Mr Flint holds a lay definition of random as a 'random event' with no purpose to it. His recall of experimentation and randomisation, in terms of chance, the use of envelopes and concealed allocation, clashes with his expectation of individualised treatment. He rationalises this by accepting that randomisation is in some way necessary:

> *Well I would have thought that [individualised treatment] was the normal way, yes. I would have thought that anyone looking at a patient would say well I think you'd be better off having this or you would be better off doing that. But I suppose on a trial as this was, they didn't want to make the decisions, they wanted to see how it came out randomly. Whether or not my problem and what*

happened to me gave them a lot of information I don't know. [Mr Flint: allocated to laser, preference for TURP]

Similarly, the term 'trial' tended to be interpreted as something being 'tried and tested' (see Mr Bowler). For example, Mr Bowler is able to believe that laser therapy is 'on trial', but has difficulty with the idea that the standard operation, TURP, is still 'on trial'. A number of non-participants (5) also believed that the trial was a process of trying out a new treatment. Similar lay definitions of trial have been found elsewhere.[58, 173]

A small number of both participants and non-participants held a partial knowledge of what the trial actually involved. For example, some saw the trial as a *'survey'* to assess their condition and supplement the standard treatment. Others assumed that this would merely entail additional paper work or tests. However, only one participant (Mr Mott) and three non-participants (Mr Flynn, Mr Allgood and Mr Frame) professed to have no knowledge of the trial at all.

Such lay interpretations of trial terminology may have been a factor in some of the non-participants receiving a treatment outside of the trial. All of the non-participants who thought they were taking part in the trial believed that individualised treatment was not inconsistent with trial participation and that they could obtain their preference, which was 'on trial', and still participate:

The surgeon did say, I take it he was a surgeon anyway, he did say that all three methods really are quite OK and they are quite happy with all three methods but er you know what suits some may not suit necessarily suit someone else. So and the impression I got was that it would be as a result of talking to me about it before it was decided [Mr Maynard: treatment preference]

Such findings have clear implications for future trials. Recruiting clinicians should not assume a shared understanding of trial terms with their patients. Trialists should discuss with recruiting clinicians the potential problems their eligible patients may have with such terms. However, providing explicit information to patients may be problematic for clinicians and can affect the

development and uptake of trials.[49] Clear definitions of trial terms such as 'randomisation' and 'trial' could perhaps also be incorporate within the patient information forms.

Treatment preferences

Few classically designed trials have attempted to take patients' preferences or views into account. However, many eligible patients have a preference for, or do not want to receive one of the treatment options available within a trial. Some refuse to participate in trials for this reason, while others may take part despite such preferences. The outcomes of these groups of patients are rarely examined, even though such perceptions can affect the internal and external validity of an RCT.[159] The importance of patient preferences varies with the condition, but may be particularly important for conditions such as benign hyperplasia of the prostate, where there is not only a choice between treatments, but a decision about whether treatment is necessary.[22]

All but four of the trial participants expressed a preference for one of the treatment options available as part of the trial. However, it is important to bear in mind that these are preferences described *after* the process of randomisation. It is not possible to know whether these preferences were present before randomisation as well as at the time of the interview within this study. Among participants, over half (10) were randomised to the treatment they appeared to prefer. Several believed that fate and destiny were involved. Others related the allocation to an expectation of receiving individualised treatment. All five of the 'true refusers' expressed a treatment preference. The majority (3) indicated that they wanted TURP because they believed this to be the standard and possibly the most effective treatment.

Preferences did seem to influence some participants' understanding of the trial in that they may have been less likely to question the method of allocation when they obtained a treatment they preferred or were not averse to. For example, Mr Bowler was determined to obtain laser and received this treatment anyway:

> *Can we just go back to the envelopes again, what would you have done if it wasn't the laser?*
>
> *I think I would have asked if I could change to the laser, I think I was set on the laser. [Mr Bowler: allocated to and preference for laser]*

It is interesting to consider what would have happened if he had been allocated to TURP. He would not have been able to obtain laser outside of the trial and this may have led him to question how he had been allocated to his treatment.

Participants' beliefs about the trial and how they had been allocated sometimes appeared to be influenced by a preference for an alternative treatment. However, it is not known to what extent such preferences are independent of or had developed as a result of their subsequent allocation to that treatment.

Eight participants appeared to have been randomised to a treatment that was not their original or rationalised preference. Two preferred TURP but were allocated to laser and five wanted either TURP or laser, but had been allocated to conservative management. This latter group had been assured that they would receive TURP (often their treatment preference) if they still both needed and desired it once they had completed the trial. This was often their reason for continuing to participate. However, two participants found their allocation to conservative management difficult to accept. Despite being able to recall the involvement of chance in their allocation, these men also wanted and expected 'treatment'. They often interpreted randomisation as an exclusion from treatment and this was often upsetting for these men:

> *You know at the moment, as I said like, the problem with this water trouble is you know four or five times every night and it's a bit annoying you know. I can go to the toilet, come downstairs and within a matter of minutes I've got to rush back upstairs. Well I think something ought to be done about it. [...] It was, it was because it was like, I naturally thought that they were going to do something about it but as I said I had no tablets or nothing for it, so that's all I can tell you. [Mr Jamison: allocated to CM but preferred 'treatment']*

Thus, even when patients agree to participate they may still have strong preferences, agreeing to take part only because there is a chance they will be

allocated to their preference or because it is their only chance of receiving the experimental treatment. The potential influences of treatment preferences on patients' understanding of the trial and motivation to participate needs to be examined by recruiting clinicians. It has been suggested that when such patients are not allocated to their preference, this may reduce their motivation and lead to biased estimates of treatment effectiveness.[109] This may have introduced bias into this trial, where the treatments options are very different. For example, a small number of these men who were allocated to conservative management became cynical and believed that treatments were being rationed. This may have increased their determination to receive the standard treatment (TURP) after they had completed the trial, which may in turn have led to an underestimation of the efficacy of that intervention. For example, Mr Mills, appears to endure the delay of conservative management in order to receive 'treatment':

> *Well, I said of course I want the operation, I am not coming here for fun you see. At the finish of the last time I was there, they said I notice you've ticked that you want the operation because she said, well if you hadn't ticked it, I would advise you to have it you see, which is you are probably here within a fortnight when you are gonna .. and sure enough, within a fortnight I was given a date and went to go in. [Mr Mills: allocated to CM, preferred active treatment]*

All five of the patients who made an active decision not to participate expressed a treatment preference. The majority wanted TURP because they believed it to be the standard and most effective. This was associated with wanting a 'successful' treatment. For the others their decision was based on a preference for a less invasive treatment (i.e. conservative management) before surgery.

Although preferences may be based on a belief that a treatment will be the most effective, quality of life is also an important factor in patients' decision making[24] and may be important for trials where the treatment options have different degrees of impact on patients' lives. This may be the case within this trial where patients could be randomised to three very different treatments.

However, from this study, it is important to concede that we cannot identify the role of preferences. It is not known to what extent preferences are independent of, or developed as a result of, subsequent allocation to that treatment. These patients' treatment allocations may have reinforced a weak preference or introduced such a preference. The clinicians' confirmation that their allocation was 'good' could also have influenced this. For example, in one case the clinician appeared to have indicated that TURP was the more effective treatment:

> *Well he said to me the normal treatment which they cut into the bladder and the penis is the most successful, the laser one he said was more of an experimental one, how would I feel about it. [Mr Stone: allocated to laser, preferred TURP]*

Trust

Trust in the clinician was found to be an overarching theme within the accounts of both participants and non-participants that appeared to exceed its current role within the literature. It had an important role in terms of both their willingness to participate and in terms of how they made sense of the trial.

The importance of trust within these accounts was often based on the patients' belief that as a *'layman'* (Mr Stone), they did not have the skills or knowledge to make an independent decision about their treatment or about trial participation, which could have repercussions for their future health. They were dependant upon the recruiting clinicians who were *'the professionals'* (Mr Stone) and as such had to be trusted. Although some had a good knowledge of randomisation, this was particularly important within the accounts of patients with low-level recall. For example, Mr Allgood's acceptance of his treatment allocation was linked to trust:

> *When you first went to see your GP did you have any expectations about what they could do for you at the hospital?*
>
> *No I seen one doctor and he said 'how would you like it done' you see well I said 'I'm not the doctor am I ' I said 'you are the person' I said 'I don't know anything about it . [Mr Allgood: a dislike of randomisation]*

This acceptance extended to participation in the trial itself. This was viewed by a number of participants in a positive way; they believed that the clinicians were acting in their best interests. By agreeing to participate in the trial, patients must take a leap of faith that the clinicians actually believe that the three treatments are equal and have no preference between the treatments being compared (equipoise). Only a small number of these patients could recall clinical equipoise and among those that did, trust was incorporated within their struggle to understand. For example, three men (Mr Jamison, Mr Brown and Mr Stone) felt that they did not have the skills or knowledge to make the decision to participate or not in the trial, they were dependant upon the expertise of the recruiting clinicians. Trust in the clinician meant that these men would accept whatever was suggested: in this case trial participation. Two men (Mr Bowler and Mr Bullock) admitted that although they would not normally agree to volunteer for anything, in this situation they felt unable to refuse.

A small number of non-participants also appeared willing to accept whatever the clinician suggested. They trusted the clinician to direct them to the 'best' treatment and this acceptance was, for a small number (4), similarly extended to a willingness to participate in the trial itself.

> *Oh yeah I would've gone through with it yeah I would've gone through with it , yeah, yeah, quite happy, yeah I don't, that's their job isn't it, they know what they're doing, that's the way I look at it, like, you know you've got to trust them really, you know to a certain extent I suppose. I've had a couple of hernia operations but I've always had good treatment so it's never worried me like you know so, I would've been quite happy to go in and have it done whatever they said, whether it would've been any good I don't know (laughs) [Mr Cullum: allocated to CM, no preference]*

Trust also has implications for how these men understand the trial. The concepts of randomisation and clinical equipoise may not make sense to patients who have implicit trust in doctors. This may lead them to re-interpret their experience of being recruited and in the case of participants, the experience of taking part, to incorporate this fundamental belief about their clinician. This may be significant within the context of the struggle to make sense of what happened to them or

what participation involved. With trust as their frame of reference, patients may be more likely to doubt that randomisation or clinical equipoise was involved and that they had been given the treatment by some other non-random means, possibly according to which was the best treatment for them.

The importance of trust in terms of participants' understanding and its influence on their willingness to agree to take part in the trial must be taken into account by trialists. To try to mitigate its effect, trust must be taken into account during the informed consent procedure. Trialists should discuss with recruiting clinicians the potential influence trust may have on eligible patients' willingness to participate in the trial. It may be that someone other than the patients' clinician, who is primarily the focus of such trust, should carry out recruitment. This also indicates that informed consent must ensure that participants have a clear understanding of clinical equipoise (this will be discussed in more detail below).

Distrust

A lack of trust in the clinicians was indicated by half (11) of the participants and this was often caused by the difficulties they had in making sense of randomisation. Surprisingly this distrust was sometimes scepticism of the method of allocation itself rather than the motives of the clinician. In some cases, randomisation was thought to be for the participant's benefit. For example, Mr Symonds believed that the clinician was giving him the best treatment in the end, even though this is not explicitly stated:

> *Yes, I thought that, exactly, right. I thought they should tell you. That's why I think they do know by what they find out what is best for you, but they don't actually come out with that..... [Mr Symonds: allocated to CM and preferred active treatment]*

He concluded that the clinician allocated him, with the envelope used 'to keep him happy':

> *I think it's obviously they decide on what, what they've found out on examining you I think they decide which is going to be best for you. That's [the envelope] only to keep you happy I think. [Mr Symonds: allocated to CM and preferred active treatment]*

He was sceptical of the use of envelopes and believed that it was a sham and that there was a hidden quota system in operation. It may be that although the envelopes led to a delay in him receiving 'treatment', this allocation did mean that he obtained his preferred treatment (TURP) at the end of the trial, rather than laser.

For the majority of those who expressed distrust, this could be tempered by a successful outcome. For example, in contrast to Mr Symonds above, where the failure to obtain his preference led to distrust, the fact that Mr Grange received his preferred treatment seems to have outweighed any suspicion of how this actually occurred:

> *I was convinced from the start that I was going to have a laser operation. I felt that that was what was going to be the result. I don't think the envelopes would've mattered. [Mr Grange: allocated to and preferred laser]*

For a small number, a lack of trust was linked to the men's difficulty in reconciling aspects of the trial design with their own experience. For example, not seeing the envelopes was perceived to be an indication that the clinician selected their treatment. Three participants were also concerned that saying no to the trial could, they believed, affect their future treatment. A few non-participants were also distrustful of some aspects of their experience. There was a general suspicion (5) that the clinicians were holding back some information about the trial or their treatment.

Being denied access to the trial (non-participants) or access to one of the treatments within the trial (participants), was often seen as a form of rationing. These patients believed they had been denied laser, the 'new' and more advanced treatment (or treatment itself if they had been allocated to conservative management). This was linked to the men's difficulty in reconciling aspects of

the trial design with their own experience. For example, when Mr Maynard did not receive treatment, he became cynical about the trial, believing he has been excluded:

> *How do you feel about the way things have turned out?*
>
> *Well I'm not very happy with the way things have turned out so far in as much as I am a little bit up in the air about what is going to happen if anything is going to happen. I came out of [clinic] assuming that all right I'm on the list for the operation so bang goes the laser, bang goes the tablets, that's the way it appears I can go now. [Mr Maynard: treatment preference]*

Cynicism is brought about by a sophisticated narrative of rationing which does follow the original rationalisation for the first use of randomisation within the MRC streptomycin trial of pulmonary tuberculosis[1]. Randomisation was initially used within this trial as an answer to the pressure faced by the MRC to distribute equitably the limited supplies of streptomycin as well as for the methodological benefits of randomisation.[2] In this trial, some of the men concluded that the 'new' more advanced technology (laser) was being rationed by the NHS, with randomisation used to achieve this equitably:

> *Do you think they had any preferences?*
>
> *The doctors? Not really, I think at the end of the day if the laser is going to free a bed a day quicker, I think it was a day quicker but you had longer at home with a catheter, that was it. If it's going to free a bed it's better for them because they can get more people in. Over the week they could get another two patients in you know which is fair comment. But it's the only way they are going to find out which treatments are the same cos I would imagine there would be a follow-up in years to come. [Mr Pierce: allocated to and preferred laser]*

These men believed that there was a quota of operations to be carried out, with each patient receiving a treatment because he attended the clinic at either the 'right' or 'wrong' time. Such beliefs were often based on these patients' experience of receiving treatment. Within this trial, laser patients were grouped together to use the machine in one surgical session, and similarly, TURP patients were also treated together.

In the design of a trial, trialists must take into account the effect simple organisational issues can have on participants' understanding of how they have been allocated to a treatment. For example, the surgery schedules here led some participants to believe that one of the treatments was being rationed in some way.

The practicalities of being in a trial

The practicalities of being in a trial in terms of the absence or occurrence of certain anticipated trial events led some participants to believe that they had not been randomised to treatment. For some, not seeing the envelopes, for example, indicated that their treatment could have been determined by the clinicians. For Mr Symonds, this was a source of distrust about the study:

> *You know, you'll know for a fact that they're giving you the choice of picking one but you're saying to yourself, no matter which one you pick, you're not getting onto the other one. [...] Yes, I think that, I don't know mind. But I think it's obviously they decide on what, what they've found out on examining you I think they decide which is going to be best for you. That's only to keep you happy I think. [Mr Symonds: allocated to CM and preferred active treatment]*

The experience of a small number of non-participants was similar. Not seeing the envelopes being used confirmed that they were not participating in the trial. However, for this group, the envelopes were often believed to provide access to the most effective or experimental treatment. For example, Mr Becker believed that he had agreed to take part, but the absence of the envelope was confirmation for him, that he had been excluded:

> *Well what they did, when that [recruiting clinician] was there[...]said if you partake of this, this survey you will fill this out and then come and see us and then you will be given an envelope and on one, you will be allowed to pick an envelope and one will say laser and one will say surgery. Whichever you pick you'll get. Well it never happened.* [*[Mr Becker: refused trial tests]*

Hence, consistency between the information given to participants and actual practice is important. In *CLasP*, patient information indicated that clinicians would open treatment allocation envelopes in front of patients. This happened during most of the participants' allocations and did help to confirm their method of allocation. However, in practice, this was not always possible and for patients who did not see the envelope, distrust could develop.

Trial protocols clearly have an impact on patients' experiences of participation. If recruiting clinicians and the trial protocol maintain that a procedure will occur, then it is important that this actually happens. What may seem an unimportant change in protocol procedure to the clinician has the potential to have a large impact on a participant's beliefs about what has happened to him.

The apparent failure of some recruiting clinicians to follow the trial protocol and open the sealed envelopes in front of participants highlights the additional issue of whether the use of envelopes to randomise patients within this trial ensured that allocation was adequately concealed. There is anecdotal evidence that some of these methods, for example, the use of envelopes, may still be open to subversion.[112] It may be that telephone randomisation would be a more satisfactory method, however, this may introduce problems of its own.

Concealed random allocation is important to avoid bias.[116] Kunz and Oxman, in their review, found that failure to conceal adequately can lead to the distortion of the treatment effects in either direction, leading to either larger or smaller effects than is actually the case.[113] For example, Schulz et al found that inadequately concealed randomisation led to estimates of effect which were 30-40% larger than trials which were believed to have adequately concealed allocation.[117] Schulz points out that although sequentially numbered, opaque, sealed envelopes, pharmacy allocation, centralised or telephone randomisation methods are generally seen to represent the minimal standards required for concealed randomisation, they are met by only a quarter of current trials.[117] The description of randomisation and the methods employed are often poorly reported in published trials, even within principal journals, making it difficult to establish

whether these studies have employed a truly random method of allocation.[13, 118] Kunz and Oxman conclude that the adequacy of concealment may be a more sensitive measure of bias within a trial than current quality assessment scales.[113]

The role of the recruiting clinician

The information patients received from their clinician often appeared to have an important influence on their interpretation of how they had been assigned to a treatment. This is indicated by the information participants reported they had received from the recruiting clinicians, the way in which these men reflected on the events of the trial and the apparent 'lottery' of participation that was observed among participants and non-participants.

Information provision

In some cases the clinician appeared to provide positive information about the allocated treatment after randomisation. This was used by participants to fill in the gaps in their understanding of why they had been allocated to that treatment. Based on the positive information they received about this treatment, these patients concluded that the clinician had provided them with the best treatment for them. To them, individualised allocation seemed a plausible theory for receiving a treatment, despite the conflicting components that this narrative contained. It was likely that the clinicians were attempting to reassure patients about their treatment rather than indicating a preference, although it could also be a way of dealing with their own unease with the process of randomisation and clinical equipoise.

> *He went away and got the envelope and opened it up yeah. No no I wasn't (laughs) I just sort of sat there and he went away and said 'I'm going to get this envelope' and brought it out and opened it in front of me and he says 'I'm happy to say that you'll be having no treatment' which he said he would have recommended anyway you know, so he said not to say that you won't you know when we check you, keep a check on you that you won't later on. So I was quite happy with that, said I'll live with that, so [Mr Cullum: allocated to CM, no preference]*

Similarly, a number of non-participants believed that they had been directed by the clinician towards one treatment. In this case, it is possible that the clinicians were merely presenting different treatment options to these patients as alternatives to the trial. We do not know whether the clinicians found this group difficult to recruit and if this was the case they may have placed more emphasis on the standard treatment.

> *So I brought this up with the consultant and the consultant I spoke to at the time he said 'we have been using it but we don't think a lot of it because it's in it's infancy and it's you know, there's a lot more work has to be done', research and so on. [Mr McCarthy: treatment preference]*

The majority of these patients wanted to be directed towards a treatment. For participants, this direction was often inferred from the clinician's descriptions of the various treatments. For a number of these men, this search for direction extended to trial participation itself:

> *When you, I look at it like this and the wife has found it the same, you want to get better so you go with it anyway, like. [Mr Brown: allocated to and preferred TURP]*

Similarly, the decision not to participate was frequently made because they received no direction from the clinician indicating that they should participate in the trial. For example, Mr Young explicitly asked for advice and in response to receiving no direction from the clinician he decided to have the option he knew most about, the standard treatment (TURP):

> *When he said 'well its entirely up to you' he didn't seem to want to make any decisions or choices for me and so I said well I thought the easiest option, the thing is to go for the operation because I've been told about it before you know, I've been up there a couple of times to see Dr T_____. [Mr Young: travel]*

This indicates that recruiting clinicians must discuss with potential participants the ways in which the trial differs from individualised treatment. Descriptions of the key abstract concepts of the RCT such as randomisation and clinical equipoise should be included within the patient information leaflet. They must

also be clear that the clinician has no treatment preference. This will be discussed in more detail below.

Reflecting on events

A few participants only realised what randomisation actually involved after they had agreed to participate. For example, Mr Formby only understood randomisation when he observed the envelope being used to allocate him to a treatment. He expected to receive the standard operation (TURP) and was surprised when this did not happen and he was allocated to laser. He makes sense of this by placing his trust in his clinician and by concluding that the clinician still has a role in deciding which treatment he receives:

> *Well, when I went there I ... I only thought that there is one thing, I thought there was just one operation, yeah. I didn't realise that you could get the laser, or you could get this er waiting thing, I thought there was just this TURP thing you know? (Yeah.) I thought that was it, you know cause I went in and she said, oh - pull such and such envelope open and I said, fair enough - that's it. [Mr Formby: allocated to CM, preferred active treatment]*

Mr Bowler admitted that he only realised that he had been randomly allocated to the treatment after he had taken part and had re-examined the patient information leaflet prior to the interview. However, this realisation may have less significance for him because he had been allocated to his preferred treatment:

> *I didn't realise it was going to be a lucky dip, these envelopes, picking one out and opening it in front of you and say it's the laser. [Mr Bowler: allocated to and preference for laser]*

> *I mean I probably just read that [patient information leaflet] sort of light heartedly. But when I read it now it does state that there may be bleeding and sometimes it ends up that the man is a lot better; where he's no different; and sometimes even worse than when he started. It tells you that now that I read it properly. [Mr Bowler: allocated to and preference for laser]*

In contrast, a number of non-participants were surprised to discover that they were not in the trial and were often adamant that they did not 'refuse'. Two non-participants appeared to agree to receive any of the available treatments and to be willing to accept trial participation.

> *Then he went on to say to me that he expected it to be more serious perhaps than it was and that would I be interested in a laser job? I said that would suit me fine. So he went, he left the room and went out, spoke to someone, came back in and said 'well it appears that it's not bad enough for a laser job' So I said well OK. So then he surprised me again and said 'now I can still put you down for an operation' So I said 'well, OK'*
>
> *In the notes it stated that you would prefer the operation...*
>
> *No that's not correct at all, I accepted what was offered to me. I was prepared to accept anything that was offered to me. [Mr Maynard: treatment preference]*

This indicates that a number of practical policies could be implemented within trials that could have helped these men to understand what the trial involved. The clinicians recruiting patients onto trials must be consistent and their behavior must reflect the information they provide to participants. For example, within this trial, the trialists expected that the protocol requirement that participants witness the use of envelopes would enhance their understanding of randomisation because they could actually see this happening in front of them. However the inability of the trialists to ensure that this happened caused confusion among many of the respondents.

The 'lottery' of participation

It is surprising that there appear to be similar levels of willingness to participate among the participants and non-participants interviewed. For example, a small number of both participants and non-participants stated that they were willing to accept whatever treatment the clinician suggested and this often extended to trial participation itself.

Although we cannot say from these data, it may be that key exchanges within the recruitment consultation may have different meanings for patients and the recruiting clinicians. Some participants confirmed that they only realised they were in a trial and what this meant once they were enrolled in the trial. In contrast, many non-participants were surprised to discover that they were not in the trial and were often adamant that they did not 'refuse'. It would be interesting to consider whether they would have ended up as participants or non-participants with a different clinician recruiting them onto the trial.

The language used to describe the treatments within the trials may have been significant. For example, the terms 'standard' and 'new' were commonly used by patients to describe their treatment. Such labels may have been obtained from their recruiting clinicians. Similarly, after allocation, some clinicians were reported to have referred to the treatment patients received as 'good' or 'best'. For patients searching for meaning and often willing to agree to any treatment the clinician suggested, this might reinforce the belief that this is the preferred treatment.

This may be associated with key questions or topics covered during the consultation. Patients often recalled that the recruiting clinician had asked which treatment they preferred. Although we do not know what actually went on during these consultations, this may have been used by the clinicians to provide patients with a way to opt out of the trial. More cynically, some clinicians may not have held personal equipoise and such key questions may have been used to direct some patients away from the trial.

There is an assumption of shared decision making within trial recruitment, but within this study we do not actually know what went on during these consultations or whether these patients made an active decision to participate or not in the trial. There may be miscommunication or it may be that the recruiting clinicians are directing some patients.

This raises an important issue about the theoretical requirement of clinical equipoise and current practice. It is important to consider how far this obligation

must extend both within the trial and more widely within clinical practice in the trial setting. It may be argued that clinical equipoise is only necessary at the point of recruitment and any reassurance the clinician provides about the treatment allocation is a good thing, although this may have an effect on outcome.[22]

However, trials must only be carried out when the evidence for treatments is balanced, and the clinician has no treatment preference. If recruiting clinicians, based on their previous experience or patient history, suspect that one treatment may be more likely to benefit a particular patient, the use of randomisation within trials represents a compromise in individual care.[42] Personal equipoise, when an individual clinician has no treatment preferences, is also an important element of patient-centred ethics within medicine. Clinicians have a duty to recommend what they believe to be the most beneficial treatment for a patient.[44]

However, as Freedman points out, such theoretical equipoise is "overwhelmingly fragile" (p.143) and can be disturbed by any slight change in the evidence which can be obtained from "the literature, uncontrolled experience, considerations of basic science and fundamental physiologic processes, and perhaps a 'gut feeling' or 'instinct'" (p.143).[43] Levine similarly argues that perfect equipoise rarely exists and that when it does, this state cannot be maintained for long.[44] As Fried notes, "is it ever likely to be the case that in a complex medical situation, the balance of harms and benefits discounted by their appropriate probabilities really does appear on the then available evidence to be in equipoise?" (p.52).[40] For a trial to be ethical, then, the research hypothesis must be simple enough to allow such a balance to exist.

The practical aspect of the dilemma of equipoise means that clinicians often have difficulty recruiting patients. A number of studies indicate that the requirement of an open discussion of clinical equipoise with patients is an obstacle for many recruiting clinicians.[43, 45-48] Many clinicians appear to prefer to trust their own experience, even if this is in conflict with the available evidence.[45, 50]

In this study, we can only suggest what went on in these consultations from the patient's perspective. However, the experience of these men and the literature

suggests that many recruiting clinicians do not enter all their eligible patients onto trials and this has implications for the realistic estimation of accrual rates and the representativeness and generalisability of trial findings.

There are a number of reasons for this. It has been suggested that the inherent conflict of taking on the dual role of investigator and physician committed to an individual patient's health is a barrier for many.[46-48, 136-138] Clinicians may fall into two groups: 'experimenters', who are primarily interested in contributing to scientific information, and therapists, for whom the patient is the main focus.[45] Recruiting oncologists have often been found to have such a 'therapist' orientation to their practice[45, 46, 75] and appeared to be deterred because they believed helping individual patients was more important than contributing to research.[46, 75] This ethical dilemma may be one of the main reasons for such difficulties[50] (see further in chapter 1).

Such findings suggest that trialists should engage in an open discussion of the issue of equipoise with recruiting clinicians. This should perhaps extend to all clinical staff likely to encounter or care for trial participants such as the research nurses working on the trial. Such members of staff may be in the position to discuss the effectiveness of treatments with patients. Thus even if trialists hold equipoise themselves they must not assume this extends to other members of the team.

Equipoise is often a barrier for recruitment and open discussion of the difficulties this requirement involves may help to minimise this problem. Before commencing the trial the issue of equipoise should be discussed with recruiting clinicians and a decision should be made as to whether individual or community equipoise is required. Trialists must also be aware that equipoise may change during the course of the trial and acknowledge that clinicians may not hold equipoise consistently; even if they hold equipoise for the patient group generally, they may not hold this for a particular patient. Even though from the clinician's perspective, a trial may have achieved equipoise, a patient's personal circumstances may mean that they have a preference for one of the treatments.[34]

Trial design may also be a barrier and it is important to incorporate the recruiting clinician's perspective when designing trials. For example, the design of some oncology trials were often believed to be too rigid for many recruiters within one US centre, and this was their rationale for excluding patients.[73] Many breast cancer clinicians have also been found to have objections to trial design,[45, 49] believing that they would enter more of their patients if trial participation were closer to normal practice.[45] Surprisingly, only a small number were deterred by the practical barriers to recruitment such as difficulty collecting data,[50, 73, 74, 78] the time involved,[73, 74] staff shortages,[74] cost,[73] travel[78] and side effects.[78] However, the majority of these studies have examined those recruiting patients onto oncology trials and it is not known to what extent these barriers are present within trials for non-life threatening conditions.

The informed consent procedure

The findings from this study indicate that the majority of these trial participants did not achieve fully informed consent. A fundamental ethical requirement of the randomised controlled trial is that patients must give their informed consent to participate. The clinicians who obtain informed consent are expected to ensure that patients receive all relevant information to make that decision.[36] When patients do not understand the implications of what they have consented to participate in, then this does not constitute truly informed consent.

There are a number of aspects of the information about the trial contained within the patient information leaflet and participant's experiences during the trial that appeared to introduce difficulties for patients in terms of their understanding of the implications for them of trial participation. For example, it appears that patients must be made aware that the treatments within the trial are equivalent- the terms 'standard' and 'new' were used to describe the treatments within the patient information leaflet and by the recruiting clinicians and thus patients often believed that the treatments were of differing effectiveness.

The majority had a treatment preference. Snowdon et al similarly found that the majority of parents preferred the 'new' experimental treatment. Most did not believe that there was uncertainty about this treatment and few were concerned about the possible risks. They were aware that the 'new' treatment was being used in other countries and thus assumed that this treatment had been proven and was safe. Treatment preferences were often based on information from the recruiting clinician, who sometimes 'inadvertently promoted a preference' (p.1349) for the 'new' treatment.[173]

This does have implications for the ethics of the trial. Patients must not agree to take part in a trial because they have false hopes or expectations of an intervention achieving a favourable outcome which is "less than reasonably likely" (p.261)[36] to happen. Such false expectations may be the result of receiving inaccurate information about a treatment's possible benefits and associated risks. This may not be deliberate, as recruiting clinicians may believe that some information is not necessary and this can occur particularly if there are cultural or socio-economic differences between the recruiting clinicians and participants.[36] Similarly, many men in this study believed that the questionnaires and tests they completed were used to establish which treatment would suit their condition and be best for them. It should be explained to patients that such examinations are used to establish that their condition is eligible for all of the treatments within the trial.

Much of the literature concludes that patients just need better or more information to help them understand participation. However, more information itself appears to be unlikely to be the entire solution because trial participation is not part of normal experience and thus does not make sense to patients. The concepts involved, such as randomisation, appear to be nonsensical to patients. The majority of the men found the concepts of the trial design and randomisation difficult to accept and developed other accounts to make sense of their experiences.

It is often stated that obtaining informed consent to participate in a trial from poorly educated patients is a 'sham'.[66] However, the data examining inequalities in the comprehension of informed consent is contradictory and as this study shows, the 'middle class' men within this trial also had differing levels of knowledge of the trial and incorporated other co-existing beliefs such as rationing, individualised treatment and fate and destiny within their rationale of how they had been allocated to their treatment.

Research examining informed consent has found that even when trials adhere to strict informed consent procedures and ensure that 'simple language' is used, this does not guarantee subjects will fully understand the implications of participation and may still have unrealistic treatment expectations.[69] A number of trials have incorporated checklists into their informed consent procedure in order to confirm recall at recruitment. However, as can be seen from these results, recall is very different from understanding.

Clearer information would be beneficial; it appeared to help some of these participants to make sense of their experience. While this study confirms the importance of providing clear and accurate patient information, it also shows that this in itself is unlikely to ensure consistent interpretation of concepts such as randomisation by participants. The patient information in this study was well received and largely accurately recalled, but patients still struggled with the concepts underlying the design and developed sometimes competing accounts. It is also not clear what impact such beliefs may have on outcome, although some found the difficulty of reconciling their views upsetting. In some cases, patients doubted the veracity of the trial.

It may be that participants need to discuss the reasons for particular methods of trial design (such as randomisation) with researchers and reflect on these in order to understand them fully enough to give true informed consent. Having the chance to discuss before making the decision to participate or not may help patients to make sense of the trial. This should be someone other than the clinicians, who were often seen as the gatekeeper to the 'best' treatment,

although it is not clear who is suitable for this role and this may only be a partial solution.

Potential trial participants should be informed specifically about the components of research that constitutes a change from the standard doctor-patient relationship. These central differences are randomisation and blinding, plus any additional clinical examinations and therapies.[66] Edwards et al conclude in their review that abstract concepts such as randomisation should receive particular attention, "since it is the conceptual scientific basis of trials rather than details of the treatments themselves which patients find hard to grasp"(p.53). It is also important that participants understand equipoise and thus have realistic expectations of the benefits of trial participation.[67]

From this study we do not know the perspective of the recruiting clinicians, however the experience of these participants and non-participants does indicate that recruitment was problematic for them. This is reflected within much of the literature where obtaining informed consent is commonly a barrier to recruitment among clinicians.[45, 47, 48, 73, 74] For many this is based on a dissatisfaction with the rigid format of the consent form[48, 73] or because it highlights their dual role as physician and investigator.[48] Such barriers can affect the development and uptake of trials. For example, the introduction of explicit regulations for a clearly defined process of informed consent describing both the risks and benefits to potential participants, led to a subsequent drop in the number of breast cancer trials being carried out.[49] Alderson concluded that providing such explicit information to patients may be problematic for clinicians.[49]

The apparent lottery as to which patients became participants in the trial indicated that these clinicians may have attempted to screen patients by trying to predict who would have difficulty with the informed consent process and thus enrol only some of their eligible patients onto trials. This is reflected in the literature[47, 75, 76] and Kee suggests that this may be because paternalism is still prevalent within medicine, with clinicians still believing that they can make the

best therapeutic decisions for their patients. However, it is highly questionable as to whether clinicians are better able to interpret medical evidence than patients themselves.[77] Given the importance of the clinician in recruiting patients onto trials, it is surprising that little research has investigated their role.[78]

Edwards et al[72] in a recent (1998) systematic review of the ethics of the RCT from the perspective of patients, the public, and healthcare professionals concluded that a surprising number of recruiting clinicians were aware that their patients did not fully understand what trial participation involved, "For many, informed consent seemed little more than a ritual" (p1212). Edwards et al conclude that there may be significant differences between trialists and ethicists as to what is ethically acceptable and suggest that there should be a greater public debate about ethics and medical research. Zwitter and Tobias similarly acknowledge that there may be a wide gap between the investigator's beliefs about informed consent and patients' actual understanding of the trial.[79]

Methodology

Understanding

Qualitative research is a collection of interpretive methods, within which no single methodology is held as superior. The overall aim is to make sense of phenomena from the perspective of the individuals within the social world, emphasising the importance of the socially constructed nature of reality by examining the social world from an interpretivist, naturalistic perspective using a variety of empirical approaches such as observation, interviews, and case studies.[223] Ethnographic methods were influential within this study. The aim was to provide a detailed description within one trial rather than attempt to generate universal principles. Thus the less structured methods of ethnography, in this case using interviews as the main method for gathering data, were most suitable for the exploratory nature of this study.

Within the present study, the theoretical approach of phenomenology advocates an exploration of trial participants' own interpretation of their experience, their

search for meaning and the importance of context in understanding their perspective. For example this allowed an examination of these men's understanding of randomisation that looked beyond the standard definition to explore their perspective and their process of rationalisation after they had had time to reflect on the actual events of the trial.

Qualitative research has shown that individuals routinely attempt to make sense of events by interpreting them in the context of their existing beliefs. Schutz introduced the idea that experience can only be accessed reflectively, not when it actually occurs. The meanings of our actions are reconstructed retrospectively on the basis of memory, they are not given in an immediate way.[228] This has important implications for interpretation, because it suggests that social scientists cannot access directly the experiences of others, but only through the interpretation of their reasons and motives.

The aim of this research strategy was to elicit participants' experiences, therefore in-depth interviews using a semi-structured checklist of topics were employed.[219, 227, 238, 239] This approach attempts to look beneath the surface of a subject in order to examine in detail what people say and explore trial participants' own interpretation of their experience and their search for meaning. Rather than using survey methods or structured interviews which rely upon assumptions about people's behaviour, this has the additional potential of revealing new areas that may not initially be anticipated.[240] Within the context of this study, this allowed me to uncover participants' actual understanding of trial terminology rather than assume such comprehension.

Reflexivity

Within qualitative research, it is important to reflect on how we present ourselves to respondents and how this may affect the interview.[227, 240] The researcher may embody a number of different identities within the interview[268] and hence a number of personal characteristics may have had an impact on the research. As a 'personable young woman'[269] interviewing men aged 55-81 years

old who were predominantly working class, I am aware that this may have introduced age, gender and social class issues into the interviews.

The age difference does appear to have had some impact on the interviews. Participants often stated that they were happy to help a student and I believe that this sympathy with my position often helped me to obtain interviews. Although I explained my status within the letter and before the interview, many also assumed I was a medical student and often saw the interviews as a way for me to learn from their experiences. Hammersley and Atkinson[270] discuss age in fieldwork relations, although the consensus is that it should not be overestimated as a factor. Robert Dingwall (personal correspondence) suggests that age has often been confused with gender and that it is important to consider whether these effects exist separately.

At the start of the interviewing process I was aware from the literature that the majority of studies were from the perspective of clinicians recruiting patients onto trials. I felt that such an approach had led to a focus onto certain areas such as gathering information to improve future recruitment rates. In addition, this work tended to utilise research methods (structured questionnaire surveys) that may have led participants to produce socially acceptable responses. For example a number of these studies used closed questions asking participants if they 'understood' what trial participation involved (see chapter 3). In response to this, I tried to distance myself from the trial and hoped that my status as 'student' would allow these men to explain what trial participation had involved for them with less anxiety about producing the 'wrong' response. Yet, as Dingwall points out, interview data are inevitably a social construct, "the respondent is still concerned to bring the occasion off in a way that demonstrates his or her competence as a member of whatever community is invoked by the interview topic" (p.59).[242] Although these men predominantly gave multiple accounts of how they had been allocated to their treatment (see chapters 5 and 6), some of the men did seek confirmation that they had 'got it right', implying that they were attempting to piece together the 'right' account of their experience.

In this way I often became a platform for them to make sense of their experiences. Although Becker is referring to those experiencing a serious illness, she argues that those undergoing 'disrupted lives' produce meaning through storytelling. When such accounts are verbalised they are shared and thus coherence and order is established from apparent chaos.[271] These men similarly appeared to be attempting to produce meaning from the 'unnatural' experience of trial participation.

Gender was also an issue. Before carrying out the interviews I did expect the men to be less willing to talk to me about their condition (benign prostatic hyperplasia). Although such issues would be part of any discussion of the trial, I felt that the focus on trial participation would mean that any reluctance to talk about their condition would not hinder the interviews. In practice, however, I found all the men eager to discuss their condition, their symptoms and how these had affected their daily life, the treatment they received and outcome. Some spoke about (unprompted) the side effects they experienced as a result of treatment, which varied from the expected (retrograde ejaculation) to more serious (impotence). I was surprised by the readiness with which these men were willing to talk to me about such issues. Many of the men remarked during the interviews that although this was a common condition that affected many of their peers, few friends were willing to discuss their experience or the treatment they had received:

> *Really that is the final, because as far as he's [clinician] concerned now I'm OK and nothing else to be done. I hope you don't mind me talking like this because there's nobody else I can talk to, to be honest with you.[Mr Stone]*

Limitations

There are clear limitations to this study because of its reliance on interview data collected after the recruitment consultation for the trial and because it examined only a small number of middle aged and elderly men asked to participate within one trial.

Although textbooks and reports of trials in journals focus on issues concerned with design, methods and results,[15, 106, 176] the patient's perspective is relatively neglected. The medical model of the clinical trial tends to assume that such experiences are not relevant to trial outcome; as Oakley points out "the doctor's task is repair by physical or chemical means, and the theory underpinning this sees the body as cellular or molecular biology, not inhabiting the same frame as the psyche, an identity, a social being intimately connected to the social and material world" (p.17).[272]

As a result there has been little work looking at patients' actual experiences of taking part in a clinical trial. However, it has been increasingly recognised that participants' perceptions of the condition, treatment and the trial can affect the internal and external validity of an RCT.[159] As Silverman and Altman acknowledge, the placebo effect suggests that other possible psychosocial influences such as preferences should be examined.[160] Thus far, little research has been undertaken to explore the views of participants and non-participants. The majority of studies within the literature have used structured, closed questions to examine the motivation for, and satisfaction with, trial participation.[218] As Edwards et al in a recent (1998) systematic review point out, the methods employed in accessing participants' motivation vary greatly between studies. Some only provide closed, forced choice questions, few allow open responses, whilst others fail to outline their rationale and hence these studies may not be comparable.[72]

The literature has predominantly examined participation to establish satisfaction with and motivation to take part in trials. Although actual participation has been examined, a fundamental problem with many of these studies is their reliance on attitudes to hypothetical trial participation. Those who have taken part in a trial may have a real and distinct difference of opinion compared to those whose responses are based on speculation.[149, 178, 182] The trials examined previously have been predominantly those that present trialists with specific ethical or recruitment issues. For example, phase I trials; trials where consent is through a

third party or trials that recruit patients with a life threatening condition such as oncology or HIV; or trials that recruit vulnerable populations such as paediatric and psychiatric trials.

At the outset of this study, the experience of participation within a pragmatic trial for a common condition had not been examined. The study reported here used qualitative research methods to elicit the perspectives of 'ordinary' middle aged and elderly men who require elective treatment for a common condition and had themselves agreed or decided not to participate in a pragmatic randomised controlled trial.

Only a small number of studies have examined the experience of trial participation and have asked participants to describe the trial in their own terms.[42, 173]. This study builds on this approach. These studies failed to adequately define recall or their assessment of understanding. Appelbaum et al give no indication as to how they defined such understanding,[42] while Snowdon et al divided parents into two main categories, those who did or did not believe that their treatment allocation was based on chance.[173] Only within this study was patient knowledge of trial design and randomisation broken down into six integral elements: the involvement of chance in their allocation, that envelopes were used to allocate treatments, that the treatment allocation was concealed, that treatments were being compared, that clinicians were uncertain about the most effective treatment, and that they were participating in an experiment. In the light of this assessment of recall, the men's subsequent understanding of the randomised controlled trial was examined.

Snowdon et al found that the recognition of the involvement of chance did not mean that these participants held a coherent model of the trial or randomisation.[173] Snowdon et al[173] and Appelbaum et al[42] argued that although participants' descriptions of the trial seemed correct, 'distortions' of the aims of randomisation were often present. I concur with this, as the men in this study similarly incorporated other non-random accounts of how they had been allocated to the treatment they received.

However, Snowdon concluded from these 'distortions' that most parents were 'confused' (p.1348) and only two parents totally accepted the use of randomisation.[173] This conclusion is common with much of the literature examining informed consent. For example, a recent systematic review of informed consent similarly suggests that the literature indicates that "patients do not always grasp what information is disclosed to them" (p.44), resulting in "defects in reasoning" (p.44).[67] However, this is a simplification of how patients make sense of their experiences of recruitment and participation in a randomised controlled trial.

In contrast, I showed that these men were striving to make sense of this confusion and sometimes developed coexisting contradictory accounts. Any confusion that arose came from their attempts to make sense of the experience by trying to piece together contradictory accounts; not from a lack of understanding of randomisation per se. Even though their narratives would not make sense to trialists, these patients made a coherent attempt to make sense of their experience of taking part (or not) in the trial. The patients' view of equipoise is also rarely examined[49] and this study shows how patients recall and struggle to make sense of this concept.

Few studies have examined the experience of non-participation. Those that do have been from the perspective of trialists in order to examine ways to improve accrual. These often examine hypothetical non-participation for trials that present ethical problems such as HIV vaccine, oncology or paediatric trials. This study uses qualitative methods to examine these non-participants' recall and understanding of what the trial involved, additionally exploring their pathways to non-participation.

The widespread use of the open-ended interview within qualitative research has been called into question.[242] Interview data are not just a series of objective facts, but active social interactions.[243] Thus interview data are social constructs developed through the participants' self-presentation and the cues the interviewer has transferred within this interaction.[242] It has been argued that

observational data, by their focus on naturally occurring events, enable the researcher to record individuals accounting to each other within their natural environment.[242] However, the aim of this study was to explore these men's accounts of their experience and understanding of trial participation and how they make sense of that verbally, rather than to reveal how people react within a specific environment. An observational approach also assumes that participants will respond to the setting in a similar way and within this study it was important to examine the distinction between what people say and what they actually do.

However, the sample of participants (22) and non-participants (11) was small. This was due to a combination of the constraints of the trial and the development of the analysis of these men's accounts, which required a number of different approaches. The interpretive strategy employed within this study was grounded theory and thus purposive sampling and an iterative, cyclical approach to the analysis of these data was carried out. This strategy did impose some constraints on the data collection. The timetable of the trial and recruitment within the trial was fixed and once I had reached the stage in the analysis of these data when more interviews would have been appropriate, the recruitment within the trial had been completed.

The analysis of these data was a laborious process. The men produced very complex and often contradictory accounts of what the trial involved and the process of participation and non-participation. There was a stage during the analysis of these accounts where on one level 'confusion' was strongly indicated, as in previous studies. However, I did not feel that this did justice to the men's accounts and it took a number of different approaches within the analysis of this data to untangle and uncover their 'struggle' to understand the trial. The analysis of these data required a detailed interrogation of the interviews, a search for negative cases and the development of detailed case histories for each of these men. At each stage these data were also independently examined by my

supervisor (JD) and followed by a detailed discussion of conflicting interpretations.

At the start of this study, published research has mainly used structured questionnaires to examine attitudes and barriers to participation in order to improve accrual. There was little detailed information on patients' understanding of key concepts such as randomisation. This qualitative study does provide insights into the complex process of recruitment and participation among a small number of men within one trial.

This study used retrospective interviews with trial participants and non-participants at different time points after they had been approached to participate in the trial. Thus within this study patients were not followed through the process of participation and the interactions between patients and the recruiting clinician were not observed. We do not know whether these patients had an actual preference or whether this was a post-facto rationalisation of their allocation. For example, some participants believed that their allocation was predestined and luckily received their preference (or rationalisation). We do not really know what would happen if these participants received a different treatment from the one they were expecting.

Observations were not carried out within this study, but future studies might benefit from examining the interaction between the recruiting clinicians and eligible patients being asked to participate in a trial. For example, we do not know what would have happened if different events had occurred during their recruitment or treatment, for example, by seeing the envelope being opened.

Interviews with recruiting clinicians were not carried out within this study and few studies have examined their experience of recruiting patients onto trials and their understanding of and the practical implementation of the ethics and methods of the randomised controlled trial. For example, given its importance to the ethics of trials, no studies have carried out an in-depth examination of the requirement of clinical equipoise, investigating the practicalities of how

recruiting clinicians define and implement this or how equipoise may change over time.

This exploratory study raises issues that might be answered by such approaches and these limitations can be rectified in future studies. Comparative studies of those who take part, drop out or refuse to participate in trials have also been suggested but have not yet been undertaken.[180, 187, 196]

Future research

Further research is required to investigate whether these interpretations are found more widely. Although this study examines a specific population, middle-aged and elderly men who had agreed to participate in a trial for a common condition, a number of these findings appear to achieve plausibility. Snowdon et al demonstrate similar findings with a population of men and women in their 20's and 30's. Although this study concluded that the majority of their sample were 'confused', they found similar patterns of trust, distrust and alternative interpretations of how they had been allocated to the treatment they received such as predestination, despite their understanding of the involvement of chance in their allocation. They also found lay interpretations of trial terms.

The methodologies employed within this study could also be used to ensure that participants receive truly informed consent and to ensure that the uncertainties regarding treatments are communicated effectively, not just meeting the official guidelines for disclosure of such risks.[151] It is not clear, however, whether greater understanding would lead to higher or lower levels of accrual to trials, but such an investigation could be linked with research attempting to incorporate patient preferences into RCTs.[160, 163, 204]

It would also be interesting to explore the influence of preferences further. Silverman and Altman suggest that misconceptions about probability may be an important aspect of preferences and thus patients must be protected from exaggerated claims about new treatments.[160] Patients may also prefer different

outcomes from those imposed by trialists.[56] However, so far trialists have been reluctant to involve patient groups in the design of trials. An investigation of the role of preferences could be achieved using longitudinal methods. Patients' views about the various treatment options could be examined prior to recruitment and after their subsequent allocation to a treatment, through to the subsequent completion of the trial.

In addition, this study indicates that the experience of recruiting clinicians and their understanding of the ethics and methods of the randomised controlled trial should be examined. This under-researched area has important implications for the external and internal validity of a trial.

APPENDIX 1

General Information for patients

Doctors and researchers in [Centre A] and [Centre B], supported by the NHS Research Directorate, are carrying out a research project to find out the best way to treat men with urinary problems. These problems are caused by an enlargement of the prostate gland which obstructs or blocks the tube (your urethra) that carries urine from your bladder. You will be asked to take part in this study if you are unable to pass urine (this often involves admission to hospital and is called acute urinary retention), or if you have urinary symptoms which are considered by yourself and the doctor to need treatment. These can be treated in hospital in a number of ways, and the aim of this research project is to find out the best method of treatment.

At the moment, two main treatments are offered to men with urinary symptoms: conservative management or an operation. Men with acute retention are usually offered an operation. New treatments are being discovered all the time, and the most promising of these is laser therapy. At the moment, doctors are not sure which of these treatments is best. Each of them has advantages and disadvantages. The CLasP study has been set up to find out which treatment has the best results and is most preferred by patients.

Conservative management. There is no surgery involved. You will be given a thorough check-up. If you wish, you can obtain information and advice about the symptoms that bother you and your fluid intake from the researcher. The latest evidence from America shows that nearly one half of men having conservative management felt better or the same after one year, and felt that they did not need surgery. All patients having conservative management will have a full review in 6 months' time. At this time, you will be able to discuss with the doctor the treatment that you need. This may be a further period of conservative

management, or surgery, depending on your symptoms and clinical need.

TURP. This is the most common treatment and involves an operation. A probe is passed into your urethra, and the inside of the prostate gland is removed by electric cutting. There is usually some bleeding. On average, you will have a catheter for 2-3 days, and be in hospital for 3-4 days. After the operation, most men find that their symptoms are considerably improved straight away, but about a quarter find that some of their symptoms are the same afterwards. A small number may find that their symptoms are worse, or experience problems following the operation - such as an infection, heavy bleeding, sexual complications.

Laser therapy. This is a new treatment and involves an operation. A probe is passed into the urethra, and the inside of the prostate gland is removed by lasers. On average, you will have to be in hospital for only 1-2 days, and you will be sent home with a catheter for about one week. Then you will need to come back to the ward for a few hours to have the catheter removed and to be checked. Men who have had this treatment so far have found that most of their symptoms are improved, not straight away but after about one month. As this is a new treatment, it is not known whether symptoms will return in the future, nor if there are any other complications.

The research

In order to compare these treatments, it is necessary to carry out a research project called a randomised controlled trial. If you agree to be involved in the study, the doctor or researcher will open a sealed envelope in front of you which will contain the name of one of the treatments. If you have urinary symptoms, you will have a one in three chance of being given conservative management, laser therapy or TURP. If you have urinary retention, you will have a one in two chance of being given laser therapy or TURP.

So that we can find out how effective the treatments are, we will ask you to complete a questionnaire about your symptoms, answer some questions, and have measurements of your flow rate and pressure in your bladder (urodynamics). Some patients will be asked if they would be willing to be interviewed about their symptoms and treatment. Approximately six months after your treatment started, you will have a full review and we will ask you to fill in another questionnaire, and to have these measurements again.

All the information you give in this study will be kept completely confidential.

You can withdraw from the study at any time without having to give any reason and your treatment will not be affected by this action. Participation in this trial is purely voluntary, and refusal to take part will not affect your future treatment in any way.

If you decide you do not wish to join the study, you will be given the standard treatment for your symptoms.

If you are willing to be included in this important study, please sign the attached Consent Form. If you have any questions or worries about being involved in the study, please contact _____.

Thank you very much for helping with this research.

APPENDIX 2

Patient Expectations and Experiences of Clinical Research

General Information

My name is Katie Featherstone and I'm a PhD student funded by the Medical Research Council, based at the Department of Social Medicine, University of Bristol.

I am carrying out a study looking at people's views of clinical trials. I am particularly interested in finding out why people choose not to take part in a clinical trial. My research is separate from the prostate trial. I will not pass anything you tell me on to staff involved in this or any other study in the Urology Unit, and nothing you tell me will affect your treatment in any way.

I understand that you are one of the many people who did not take part in a recent trial of treatments for prostate problems. Your name has been chosen at random from those people attending the Urology Institute who did not want to take part. Your consultant has given me permission to approach you.

I hope that you will be able to take part in my study. I do not want to persuade you to change your mind about taking part, I would just like to ask you some questions. There are very few studies looking at why people choose not to take part in clinical trials, and your views and feelings will give me an insight into how people view clinical research.

The interview will take approximately half an hour of your time and the information you give will not be used in any way that could identify you

personally. The Southmead Medical Research Ethics Committee has approved this study.

All the information you give in this study will be kept completely confidential.

You can withdraw from this study at any time without having to give any reason and your treatment will not be affected by this action. Participation in my study is purely voluntary, and refusal to take part will not affect your future treatment in any way.

I will contact you in the next few days to see if you are willing to take part.

If you have any questions or worries about taking part, please contact me, Katie Featherstone (tel: 0117 928 7395) or my supervisor Dr Jenny Donovan (tel: 0117 928 7214) at the Department of Social Medicine, Canynge Hall, Whiteladies Road, Clifton, Bristol BS8 2PR.

Thank you for helping me with my research.

Katie Featherstone

PhD Student

Patients Expectations and Experiences of Clinical Trials

Patient interview schedule

How did you find out about your prostate condition / urinary symptoms?
What has happened since you started attending the clinic

Did you have any initial expectations of what the treatment would involve/ the success of the available treatments?
Did you have any ideas about which treatment you wanted?
What kind of choices did you think you would be given?

What happened when you attended the clinic?
Were you asked if you wanted to take part in research / study/ of treatments for prostate problems: Can you remember/tell me anything about that?
What did you think about this option?

Looking back, what did taking part in this would involve?
What were your initial expectations?

Were you able to ask questions about this/the research
Did you speak to /ask for advice from anyone before you made a decision
Were you given any written information explaining what taking part would involve- what did that say

How did taking part in this research compare with the other treatment options
Did you have any worries about taking part [in the research]
What were you told about the different treatments [offered as part of the research]?

Who decided which treatment you should receive?
How was the doctor going to decide which treatment to give you?

If you had a free choice, which treatment would you have chosen?

how did you come to that decision / why was that
How do you think that treatment compared to the other options [that were part of the research study]
had you heard anything about that treatment

Why did you decide not to take part in the research?
can you tell me more about that
Did you have any concerns about taking part?

Who decided which treatment you should receive
How was this decided?
Were you able to choose which treatment to
How did you decide which treatment

Why do you think this clinic does these sorts of studies?
Who do you think benefits the most from these research studies?
Why did you think the doctor asked you?
What do you know about medical research in general?

Looking back, how do you feel about the way things have turned out?

REFERENCES

1. Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. BMJ 1948;**2**:779-82.

2. Yoshioka A. Use of randomisation in the Medical Research Council's clinical trial of streptomycin in pulmonary tuberculosis in the 1940s. BMJ 1998;**317**:1220-3.

3. Editorial. The controlled therapeutic trial. BMJ 1948;**2**:791-2.

4. Hill AB. Principles of medical statistics:1. The aim of the statistical method. Lancet 1937;**1**:41-3.

5. Hinshaw HC, Feldman WH. Evaluation of chemotherapeutic agents in clinical tuberculosis: a suggested procedure. Am Rev Tuberc 1944;**50**:202-13.

6. Amberson JB, McMahon BT, Pinner M. A clinical trial of sanocrysin in pulmonary tuberculosis. Am Rev Tuberc 1931;**24**:401-35.

7. MRC Whooping-Cough Immunization Committee. The prevention of whooping-cough by vaccination. BMJ 1951;**1**:1463-71.

8. Doll R. Controlled trials: the 1948 watershed. BMJ 1998;**317**:1217-20.

9. Hrobjartsson A, Gotzche PC, Gluud C. The controlled clinical trial turns 100 years: Fibiger's trial of serum treatment of diptheria. BMJ 1998;**317**:1243-5.

10. Fibiger J. On serum treatment of diptheria. Hospitalstiende 1898;**6**:309-25.

11. Chalmers I. Unbiased, relevant and reliable assessments in health care. BMJ 1998;**317**:1267-8.

12. Peto R, Baigent C. Trials: the next 50 years. BMJ 1998;**317**:1170-1.

13. Jadad AR. Randomised Controlled Trials, A user's guide. London: BMJ Books, 1998.

14. Cochrane AL. Effectiveness and efficiency: random reflections on health services. London: BMJ and Nuffield Provincial Hospitals Trust, 1989.

15. Pocock SJ. Clinical Trials: a practical approach. Chichester: A Wiley, 1983.

16. Minert CL. Clinical Trials. Oxford: Oxford University Press, 1986.

17. Schwartz D, Flamant R, Lellouch J. Clinical Trials. London: Academic Press, 1980.

18. Altman DG. Practical statistics for medical research. London: Chapman and Hall, 1991.

19. Cranberg L. Evaluating new treatments. BMJ 1998;**317**:1261.

20. Starzl TE, Donner A, Eliasziw M, Meier P, Fung JJ, McMichael JP, et al. Randomised trialomania? The multicentre liver transplant trials of tacrolimus. Lancet 1995;**346**:1346-50.

21. Wynne A. Is it any good? The evaluaton of therapy by participants in a clinical trial. Soc Sci Med 1989;**29.No.11**:1289-97.

22. McPherson K. The best and the enemy of the good: randomised controlled trials, uncertainty, and assessing the role of patient choice in medical decision making. J Epidemiol Community Health 1994;**48**:6-15.

23. Zelen M. A new design for randomized clinical trials. N Engl J Med 1979;**300**:1242-5.

24. McPherson K, Britton AR, Wennberg JE. Are randomized controlled trials controlled? Patient preferences and unblind trials. J R Soc Med 1997;**90**:652-6.

25. The Philadelphia Enquirer. Author dug into story of testing on inmates. Lifestyle and entertainment magazine.

26. Hornblum AM. Acres of skin: Human experiments at Holmesburg Prison; A true story of abuse and exploitation in the name of medical science. US: Routledge, 1998.

27. The Guardian. Inquiry into experiment on babies.

28. Jones J. Government sets up inquiry into ventilation trial. BMJ 1999;**318**:553.

29. Katz J. The Nuremberg Code and the Nuremberg Trial: a reappraisal. JAMA 1996;**276**:1662-6.

30. The 41st World Medical Assembly. Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects.

31. General Medical Council. Good Medical Practice. London.

32. Advisory Committee on Human Radiation Experiments. Reserch ethics and the medical profession. JAMA 1996;**276(5)**:403-9.

33. Medical Research Council. MRC guidelines for good clinical practice in clinical trials. London.

34. Kodish E, Lantos JD, Siegler M. Ethical considerations in randomized controlled clinical trials. Cancer 1990;**(supplement)**:2400-4.

35. Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL. Implications of socio-cultural contexts for the ethics of clinical trials. 1st ed. v. 1(9). Basingstoke,UK: Health Technology Assessment NHS R&D HTA Programme, 1997.

36. De Castro L. Exploitation in the use of human subjects for medical experimentation: a re-examination of basic issues. Bioethics 1995;**9(3/4)**:259-68.

37. Lawrence W. Patient selection for clinical trials. Risks versus benefits and quality of life issues. Cancer 1993;**72(9)**:2798-800.

38. Herxheimer A. Clinical trials: two neglected ethical issues. J Med Ethics 1993;**19**:211,218.

39. The Cochrane Library. Cochrane Collaboration, Issue 3. Oxford: Update Software.

40. Fried C. Medical experimentation: personal integrity and social policy. 5th ed. New York: American Elsevier, 1974.

41. Lilford RJ, Jackson J. Equipoise and the ethics of randomisation. J R Soc Med 1995;**88**:552-9.

42. Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False hopes and best data: consent to research and the theraputic misconception. Hastings Cent Report 1987;**April**:20-4.

43. Freedman B. Equipoise and the ethics of clinical reserch. N Engl J Med 1987;**317(3)**:141-5.

44. Levine RJ. Ethics of clinical trials. Do they help the patient? Cancer 1993;**72(9)**:2805-10.

45. Taylor KM, Kelner M. Interpreting physician participation in randomized clinical trials: The physician orientation profile. J Health Soc Behav 1987;**28**:389-400.

46. Taylor KM. Integrating conflicting professional roles: physician participation in randomized clinical trials. Soc Sci Med 1992;**35(2)**:217-24.

47. Taylor KM, Margolese RG, Soskoline CL. Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer. N Engl J Med 1984;**310 (21)**:1363-7.

48. Taylor KM, Kelner M. Informed consent: the physicians perspective. Soc Sci Med 1987;**24(2)**:135-43.

49. Alderson P. Equipoise as a means of managing uncertainty: personal, communal and proxy. J Med Ethics 1996;**22**:135-9.

50. Hunter CP, Frelick RW, Feldman AR, Bavier AR, Dunlap WH, Ford L, et al. Selection factors in clinical trials: Results from the community clinical oncology program physician's patient log. Cancer Treat Rep 1987;**71(6)**:559-65.

51. Charlton BG. Randomized clinical trials: the worst kind of epidemiology? Nature Medicine 1995;**1(11)**:1101-2.

52. Gifford F. Community-equipoise and the ethics of randomized clinical trials. Bioethics 1995;**9(2)**:127-48.

53. Johnson N, Lilford RJ, Brazier W. At what level of collective equipoise does a clinical trial become ethical. J Med Ethics 1991;**17**:30-4.

54. Chard JA, Lilford RJ. The use of equipoise in clinical trials. Soc Sci Med 1998;**00**:1-8.

55. Segelov E, Tattersall MHN, Coates AS. Redressing the balance- the ethics of not entering an eligible patient onto a randomised clinical trial. Ann Oncol 1992;**3**:103-5.

56. Prestifilippo J, Antman K, Berkman BJ, Kaufman D, Lantos J, Lawrence W, et al. The ethical treatment of cancer. What is right for the patient? Cancer 1993;**72(9)**:2816-9.

57. Gifford F. The conflict between randomized clinical trials and the therapeutic obligation. J Med Philos 1986;**11**:347-66.

58. Roberson NL. Clinical trial participation. Viewpoints from racial/ethnic groups. Cancer Suppl 1994;**74**:2687-91.

59. Friedman MA, Cain DF. National Cancer Institute sponsored cooperative clinical trials. Cancer 1990;**(Suppl)**:2376-82.

60. Rothman KJ. Placebo mania. BMJ 1996;**313**:3-4.

61. Collier J. Confusion over the use of placebos in clinical trials. BMJ 1995;**311**:821-2.

62. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. N Engl J Med 1994;**331(6)**:394-8.

63. Hill AB. Medical ethics and controlled trials. BMJ 1963;**1**:1043-9.

64. Lantos J. Informed consent. The whole truth for patients? Cancer 1993;**72(9)**:2811-5.

65. Hellman S. Randomized clinical trials and the doctor-patient relationship. Cancer Clin Trials 1979;**2**:189-93.

66. Editorial. Your baby is in a trial. BMJ 1995;**245**:805-6.

67. Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J. Ethical issues in the design and conduct of randomised controlled trials. Health Technology Assessment 1998;**2(15)**.

68. Searight HR, Miller CK. Remembering and interpreting informed consent: a qualitative study of drug trial participants. J Am Board Fam Prac 1996;**9(1)**:14-22.

69. Harth SC, Thong YH. Parental perceptions and attitudes about informed consent in clinical research. Soc Sci Med 1995;**41**:1647-51.

70. Olver IN, Buchanan L, Laidlaw C, Poulton G. The adequacy of consent forms for informing patients entering oncological clinical trials. Ann Oncol 1995;**6**:867-70.

71. Beecham L. GMC advises doctors on seeking consent. BMJ 1999;**318**:553.

72. Edwards SJL, Lilford RJ, Hewison J. The ethics of randomised controlled trials from the perspectives of patients, the public, and healthcare professionals. BMJ 1998;**317**:1209-12.

73. Benson III AB, Pregler JP, Bean JA, Rademaker AW, Eshler B, Anderson K. Oncologists' reluctance to accrue patients onto clinical trials: an Illinois cancer centre study. J Clin Oncol 1991;**9(11)**:2067-75.

74. Smyth JF, Mossman J, Hall R, Hepburn S, Pinkerton R, Richards M, et al. Conducting clinical trials in the new NHS: the model of cancer. BMJ 1994;**309**:457-61.

75. Taylor KM, Feldstein ML, Skeel RT, Pandya KJ, Hg P, Carbone PP. Fundamental dilemmas of the randomized clinical trial process: Pesults of a survey of the 1,737 Eastern Cooperative Oncology Group Investigators. J Clin Oncol 1994;**12(9)**:1796-805.

76. Siminoff LA, Fetting JH, Abeloff MD. Doctor-patient communication about breast cancer adjuvant therapy. J Clin Oncol 1989;**7(9)**:1192-200.

77. Kee F. Patients' perspectives and perceptions of benefit. BMJ 1996;**312**:958-60.

78. Spaight SJ, Nash S, Finison LJ, Patterson WB. Medical oncologists' participation in cancer clinical trials. Progress Clin Biol Res 1984;**156**:49-61.

79. Zwitter M, Tobias JS. A survey of the ethical considerations in randomised trials for lung cancer. Lung Cancer 1998;**19**:197-210.

80. Tobias JS, Souhami RL. Fully informed consent can be needlessly cruel. BMJ 1993;**307**:1199-201.

81. Wong JG. Open discussion promotes trust. BMJ 1993;**307**:1105.

82. Walsworth-Bell JP. Doctors should admit uncertainty. BMJ 1993;**307**:1105.

83. Jensen AB, Madsen B, Andersen P, Rose C. Information for cancer patients entering a clinical trial- an evaluation of an information strategy. Eur J Cancer Care 1993;**29**:2235-8.

84. White DR, Muss HB, Michielutte R, Cooper MR, Jackson DV, Richards F, et al. Informed consent: patient information forms in chemotherapy trials. Am J Clin Oncol 1984;**7**:183-90.

85. Kent G. Shared understandings for informed consent: the relevance of psychological research on the provision of information. Soc Sci Med 1996;**43 (10)**:1517-23.

86. Guadagnoli E, Ward P. Patient participation in decision-making. Soc Sci Med 1998;**47 No.3**:329-39.

87. Minogue BP, Palmer-Fernandez G, Udell L, Waller BN. Individual autonomy and the double-blind controlled experiment: the case of desperate volunteers. J Med Philos 1995;**20**:43-55.

88. Logue G, Wear S. A desperate solution: individual autonomy and the double-blind controlled experiment. J Med Philos 1995;**20**:57-64.

89. Thornton HM. Breast cancer trials: a patient's viewpoint. Lancet 1992;**339: Jan 4**:44-5.

90. McNeill P. Paying people to participate in research: why not? Bioethics 1997;**11(5)**:390-6.

91. Tindall G. Patient research and informed consent. J R Soc Med 1990;**83**:337-9.

92. Kaufman D. Cancer therapy and the randomised clinical trial. Cancer 1993;**72**:2801-4.

93. Stiller CA. Centralised treatment, entry to trials and survival. Br J Cancer 1994;**70**:352-62.

94. Davis S, Wright PW, Schulman SF, Hill LD, Pinkham RD, Johnson LP, et al. Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. Cancer 1985;**56**:1710-8.

95. Reiser J, Warner JO. The value of participating in an asthma trial. Lancet 1985;**1**:206-7.

96. Karjalainen S, Palva I. Do treatment protocols improve end results? A study of survival of patients with multiple myeloma in Finland. BMJ 1989;**299**:1069-72.

97. Harth SC, Thong YH. Sociodemographic and motivational characteristics of parents who volunteer their children for clinical research: a controlled study. BMJ 1990;**300**:1372-5.

98. Howard JM, DeMets D, The BHAT Research Group. How informed is informed consent? The BHAT experience. Control Clin Trials 1981;**2**:287-303.

99. Flanery M, Gravdal J, Hendrix P, Hoffman W, King P, May D, et al. Just sign here... Dacota Journal of Medicine 1978;**31**:33-7.

100. The DCCT Research Group. Implementation of a multicomponent process to obtain informed consent in a diabetes control and complications trial. Control Clin Trials 1989;**10**:83-96.

101. Sussman EJ, Dorn LD, Fletcher JC. Participation in biomedical research: the consent process as viewed by children, adolescents, young adults and physicians. J Pediatr 1992;**121**:547-52.

102. Goodman NW, Cooper GM, Malins AF, Prys-Roberts C. The validity of informed consent in a clinical study. Anaesthesia 1984;**39**:911-6.

103. Gallet M, Aupetit JF, Servan E, Lastaevel M, Lopez M, Chassoux G. Informed consent: what information remains at the end of a therapeutic trial? Arch Mal Coeur 1994;**87**:39-45.

104. Dal-Re. Good clinical practice in clinical trials: the responsibilities of the investigator. Survey of 827 hospital physicians (and II). Patient consent. Med Clin (Barc) 1993;**100(11)**:423-7.

105. Lynoe N, Sandlund M, Dahlqvist G, Jacobsson L. Informed consent: study of quality of information given to participants in a clinical trial. BMJ 1991;**303**:610-3.

106. Senn S. Statistical Issues in Drug Development. Chichester: John Wiley and Sons, 1997.

107. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Chron Dis 1967;**20**:637-48.

108. Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. Int J Epi 1992;**21**:837-41.

109. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. BMJ 1989;**299**:313-5.

110. Lumley J, Lester A, Renou P, Wood C. A failed RCT to determine the best method of delivery for very low birth weight infants. Control Clin Trials 1985;**6**:120-7.

111. McLean PD. The effect of informed consent on the acceptance of random treatment assignment in a clinical population. Behaviour Therapy 1980;11:129-33.

112. Schulz KF. Subverting randomization in controlled trials. JAMA 1995;**274(18)**:1456-8.

113. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. BMJ 1998;**317**:1185-90.

114. Edwards SJL, Braunholtz DA, Lilford RJ, Stevens AJ. Ethical issues in the design and conduct of cluster randomised controlled trials. BMJ 1999;**318**:1407-9.

115. Togerson D, Campbell M. Unequal randomisation can improve the economic efficiency of clinical trials. J Health Serv Res Policy 1997;**2(2)**:81-5.

116. Torgerson DJ, Roberts C. Randomisation methods: concealment. BMJ 1999;**319**:375-6.

117. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;**273(5)**:408-12.

118. Altman DG, Dore CJ. Randomisation and baseline comparisons in clinical trials. Lancet 1990;**335**:149-55.

119. Russell I. Evaluating new surgical procedures. BMJ 1995;**311**:1243.

120. Greenberg RP, Fisher S. Seeing through the double-masked design: A commentary. Control Clin Trials 1994;**15**:244-6.

121. Vere DW. Ethics of clinical trials. In: Good, editor. The priniples and practice of clinical trials. England:, 1976.

122. McConnell JD, Barry MJ, Bruskewitz RC, Bueschen AJ, Denton SE, Holtgrewe HL, et al. Benign prostatic hyperplasia:diagnosis and treatment. Maryland US: AHCPR Publication, 1994.

123. Aspinall RL, Goodman NW. Denial of effective treatment and poor quality of clinical information in placebo controlled trials of ondansetron for postoperative nausea and vomiting: a review of published trials. BMJ 1995;**311**:844-6.

124. Welton AJ, Vickers MR, Cooper JA, Meade TW, Marteau TM. Is recruitment more difficult with a placebo arm in randomised controlled trials? A quasirandomised, interview based study. BMJ 1999;**318**:1114-7.

125. McCusker J, Wax A, Bennett JM. Cancer patient accessions into clinical trials. A pilot investigation into some patient and physician determinants of entry. Am J Clin Oncol 1982;**5**:227-36.

126. Schwartz CE, Fox BH. Who says yes? identifying selection biases in a psychosocial intervention study of multiple sclerosis. Soc Sci Med 1995;**40(3)**:359-70.

127. The Standards of Reporting Trials Group. A proposal for structured reporting of randomized controlled trials. JAMA 1994;**272(24)**:1926-31.

128. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA 1996;**276(8)**:637-9.

129. Leventhal H, Nerenz DR, Leventhal EA, Love RR, Bendena LM. The behavioural dynamics of clinical trials. Prev Med 1991;**20**:132-46.

130. Dahan R, Caulin C, Figea L, Kanis JA, Caulin F, Segrestaa JM. Does informed consent influence therapeutic outcome? A clinical trial of the hypnotic activity of placebo in patients admitted to hospital. BMJ 1986;**293**:363-4.

131. Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side effects. Clin Pharmacol Ther 1987;**42(3)**:250-3.

132. Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. Lancet 1997;**350**:326-9.

133. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;**17**:1-12.

134. Moher D, Jadad AR, Tugwell P. Assessing the quality of randomized controlled trials. Int J Technology Assess Health Care 1996;**12(2)**:195-208.

135. Evans M, Pollock AV. Trials on trial: A review of trials of antibiotic prophylaxis. Arch Surg 1984;**119**:109-13.

136. Hjorth M, Holmberg E, Rodjer S, Taube A, Westin J. Physicians' attitudes toward clinical trials and their relationship to patient accrual in a Nordic multicenter study of myeloma. Control Clin Trials 1996;**17**:372-86.

137. Twomey JG. Investigating pediatric HIV research ethics in the field. Weston J Nurs Res 1994;**16(4)**:404-13.

138. Kahn J. Success and sadness. JAMA 1998;**280(1)**:89.

139. Farrell B. Efficient management of randomised controlled trials: nature or nurture. BMJ 1998;**317**:1236-9.

140. Wermeling DP, Selwitz AS. Current issues surrounding women and minorities in drug trials. Ann Pharmacother 1993;**27**:904-11.

141. McCabe MS, Varricchio CG, Padberg RM. Efforts to recruit the economically disadvantaged to national clinical trials. Semin Oncol Nurs 1994;**10 No.2 (May)**:123-9.

142. Mettlin C, Cummings KM, Walsh D. Risk factor and behavioural correlates of willingness to participate in cancer prrevention trials. Nutr Cancer 1985;**7(4)**:189-98.

143. Millon-Underwood S, Sanders E, Davis M. Determinants of participation in state-of-the-art cancer prevention, early detection/screning, and treatment trials among African-Americans. Cancer Nurs 1993;**16(1)**:25-33.

144. Bartholow BN, Macqueen KM, Douglas JMJ, Buchbinder S, McKirnan D, Judson FN. Assessment of the changing willingness to participate in phase III HIV vaccine trials among men who have sex with men. J Acquir Immune Defic Syndr Hum Retrovirol 1997;**16(2)**:108-15.

145. Gross M, Seage GR, Mayer KH, Goldstein RS, Losina E, Wold C. Interest among gay/bisexual men in Greater Boston in participating in clinical trials of preventative HIV vaccines. J Acquir Immune Defic Syndr Hum Retrovirol 1996;**12**:406-12.

146. Douglas J JM, Judson FN, Parks JP, Buchbinder S, McKirnan D. Participation of homosexual/bisexual men in preventive HIV vaccine trials: baseline attitudes and concerns and predicted behaviours during trials. AIDS Res Hum Retroviruses 1994;**10(suppl2)**:257-60.

147. Vlahov D, Astemborski J, Solomon L, Galai N, Basarab L, Nelson KE. Interest in HIV vaccines among injection drug users in Baltimore, Maryland. AIDS Res Hum Retroviruses 1994;**10(Suppl2)**:265-8.

148. Autret E, Dutertre JP, Barbier P, Jonville AP, Pierre F, Berger C. Parental opinions about biomedical research in children in Tours, France. Dev Pharmacol Ther 1993;**20**:64-71.

149. Geraard MJ, Rouillon F, Miller HD, Dreyfus JP. Consent for clinical trials in psychiatry: results of a population survey. Clin Research & Reg Affairs 1995;**12(3)**:193-209.

150. Slevin M, Mossman J, Bowling A, Leonard R, Steward W, Harper P, et al. Volunteers or victims: patients' views of randomised cancer clinical trials. Br J Cancer 1995;**71**:1270-4.

151. Turner CF, Sheon AR. Behavioural studies relevant to vaccine trial preparation: an introduction. AIDS Res Hum Retroviruses 1994;**10(2)**:273-6.

152. Fetting JH, Siminoff LA, Piantadosi S, Abeloff MD, Damron DJ, Sarsfield AM. Effect of patients' expectations of benefit with standard breast cancer adjuvant chemotherapy on participation in a randomized clinical trial: A clinical vignette study. J Clin Oncol 1990;**8 (9)**:1476-82.

153. Streiner DL, Norman GR. Health measurement scales. A practical guide to their development and use. Oxford: Oxford university Press, 1989.

154. Roland M, Torgerson D. Understanding controlled trials: what outcomes should be measured? BMJ 1998;**317**:1075-80.

155. Sanders C, Egger M, Donovan J, Tallon D, Frankel S. Reporting of quality of life in randomised controlled trials:bibliographic study. BMJ 1998;**317**:1191-4.

156. Gill TM. Quality of life assessment:values and pitfalls. J R Soc Med 1995:680-2.

157. Naslund GK, Fredrikson M, Hellenius M, de Faire U. Determinants of compliance in men enrolled in a diet and exercise intervention trial: a randomized controlled trial. Patient Education and Counseling 1996;**29**:247-56.

158. Mullen PD, Green LW, Persinger GS. Clinical trials of patient education for chronic conditions: A comparative meta-analysis of intervention types. Prev Med 1985;**14**:753-81.

159. Angell M. Patients' preferences in randomized clinical trials [editorial]. N Engl J Med 1984;**310**:1385-7.

160. Silverman WA, Altman DG. Patients' preferences and randomised trials. Lancet 1996;**347**:171-4.

161. Barofsky I, Sugarbaker PH. Determinants of patient nonparticipation in randomized clinical trials for the treatment of sarcomas. Cancer Clin Trials 1979;**2**:237-46.

162. Berry H, Bloom B, Mace BEW, Hamilton EBD, Fernandes L, Molloy M, et al. Expectation and patient preference - does it matter? J R Soc Med 1980;**73**:34-8.

163. Kassirer JP. Incorporating patients' preferences inot medical decisions. N Engl J Med 1994;**330(26)**:1895-6.

164. Korn EL, Baumbrind S. Randomised clinical trials with clinician-preferred treatment. Lancet 1991;**337**:149-52.

165. Widder J. Randomising means, not aims in clinical trials. Lancet 1994;**343**:359.

166. Thornton H. Patients' preferences and randomised trials. Lancet 1994;**344**:689.

167. Henshaw RC, Naji SA, Russell IT, Templeton AA. Comparison of medical abortion with surgical vacuum aspiration: women's preferences and acceptability of treaatment. BMJ 1993;**307**:714-7.

168. Nicolaides K, de Lourdes Brizot M, Patel F, Snijders R. Comparison of chronic villus sampling and amniocentesis for fetal karyotyping at 10-13 weeks gestation. Lancet 1994;**344**:435-9.

169. Cooper KG, Grant AM, Garratt AM. The impact of using a partially randomised patient preference design when evaluating alternative managements for heavy menstrual bleeding. Br J Obstet Gynaecol 1997;**104(12)**:1367-73.

170. King M, Broster G, Lloyd M, Horder J. Controlled trials in the evaluation of counselling in general practice. Br J Gen Pract 1994;**44**:229-32.

171. Gossop M, Johns A, Green L. Opiate withdrawal: inpatient versus outpatient programmes and preferred versus random assignment to treatment. BMJ 1986;**293**:103-4.

172. Cancer Research Campaign Working Party in Breast Conservation. Informed consent: ethical, legal, and medical implications for doctors and patients who participate in randomised clinical trials. BMJ 1983;**286**:1117-21.

173. Snowdon C, Garcia J, Elbourne D. Making sense of randomization: Responses of parents of critically ill babies to random allocation of treatment in a clinical trial. Soc Sci Med 1997;**45**:1337-55.

174. Levene M, Wright I, Griffiths G. Is informed consent in neonatal randomised controlled trials ritual? [letter]. Lancet 1996:475.

175. Naylor CD, Llewellyn-Thomas HA. Can there be a more patient-centred approach to determining clinically important effect sizes for randomized treatment trials. J Clin Epidemiol 1994;**47**:787-95.

176. Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. BMJ 1996;**313**:570-1.

177. Cassileth BR, Lusk EJ, Miller DS, Hurwitz S. Attitudes toward clinical trials among patients and the public. JAMA 1982;**248**:968-70.

178. Kemp N, Skinner E, Toms J. Randomized clinical trials of cancer treatment- a public opinion survey. Clin Onc 1984;**10**:155-61.

179. Mackillop WJ, Palmer MJ, O'Sullivan B, Ward GK, Steele R, Dotsikas G. Clinical trials in cancer: the role of surrogate patients in defining what constitutes an ethically acceptable cliinical experiment. Br J Cancer 1989;**59**:388-95.

180. Corbett F, Oldham J, Lilford R. Offering patients entry in clinical trials: preliminary study of the views of prospective participants. J Med Ethics 1996;**22**:227-31.

181. Bevan EG, Chee LC, McGhee SM, McInnes GT. Patients' attitudes to participation in clinical trials. Br J Clin Pharmacol 1993;**35**:204-7.

182. Saurbrey N, Jensen J, Rasmussen PE, Gjorup T, Guldager H, Riis P. Danish patients' attitudes to scientific-ethical questions. An interview study focusing theraputic trials. Acta Med Scand 1984;**215**:99-104.

183. Macqueen KM, Buchbinder S, Douglas JM, Judson FN, Mckirnan DJ, Barthalow B. The decision to enroll in HIV vaccine efficacy trials: concerns elicited from gay men at increased risk of HIV infection. AIDS Res Hum Retroviruses 1994;**10(Suppl2)**:261-4.

184. Jenkins RA. Integrating qualitative and quantitative information in understanding willingness to participate in HIV preventive vaccine trials (Abstract). AIDS Res Hum Retroviruses 1994;**10(Suppl2)**:289.

185. Wiley JA, Osmond D, Page K, Garrett K, Winkelstein W. Willingness of young gay and bisexual men to participate in phase III vaccine trials: baseline survey results from the San Francisco Young Men's Health Study. AIDS Res Hum Retroviruses 1994;**10,suppl 2**:s269.

186. Llewellyn-Thomas HA, McGreal MJ, Thiel EC, Fine S, Erlichman C. Patients' willingness to enter clinical trials: Measuring the association with perceived benefit and preference for decision participation. Soc Sci Med 1991;**32**:35-41.

187. Mattson ME, Curb JD, McArdle R, and the AMIS and BHAT Research Groups. Participation in a clinical trial: The patients' point of view. Control Clin Trials 1985;**6**:156-67.

188. Henzlova MJ, Blackburn GH, Bradley EJ, Rogers WJ. Patient perception of a long-term clinical trial: Experience using a close-out questionnaire in the studies of left-ventrincular dysfunction (SOLVD) trial. Control Clin Trials 1994;**15**:284-93.

189. DeLuca SA, Korcuska LA, Oberstar BH, Rosenthal ML, Welsh PA, Topol EJ. Are we promoting true informed consent in cardiovascular trials? J Cardiovasc Nurs 1995;**9(3)**:54-61.

190. Suchanek Hudmon K, Stoltzfus C, Chamberlain RM, Lorimor RJ, Steinbach G, Winn RJ. Participants' perceptions of a phase I colon cancer chemoprevention trial. Control Clin Trials 1996;**17**:494-508.

191. Daugherty C, Ratain MJ, Grochowski E, Stocking C, Kodish E, Mick R, et al. Perceptions of cancer patients and their physicians involved in phase I trials. J Clin Oncol 1995;**13**:1062-72.

192. Hassar M, Weintraub M. "Uninformed" consent and the wealthy volunteer: an analysis of patient volunteers in a clinical trial of a new annti-inflammatory drug. Clin Pharmacol Ther 1976;**20(4)**:379-86.

193. Charles C, Redko C, Whelan T, Gafni A, Reyno L. Doing nothin is no choice: lay constructions of treatment decision-making among women with early-stage breast cancer. Soc Sci Med 1998;**20(1)**:71-95.

194. Tabak N. Decision making in consenting to experimental therapy. Cancer Nurs 1995;**18(2)**:89-96.

195. Rodenhuis S, Van Den Heuvel WJA, Annyas AA, Koops HS, Sleijfer DTH, Mulder NH. Patient motivation and informed consent in a Phase I study of an anticancer agent. Eur J Cancer Clin Oncol 1984;**20,No.4**:457-62.

196. Cox K, Avis M. Psychosocial aspects of participation in early anticancer drug trials. Report of a pilot study. Cancer Nurs 1996;**19(3)**:177-86.

197. Stetz KM. Survival work: the experience of the patient and the spouse involved in experimental treatment for cancer. Semin Oncol Nurs 1993;**9 (2)**:121-6.

198. Tindall B, Forde S, Ross MW, Goldstein D, Barker S, Cooper DA. Effects of two formats of informed consent on knowledge amongst persons with advanced HIV disease in a clinical trial of didanosine. Patient Education and Counselling 1994;**24**:261-6.

199. Ryan L. 'Going public' and 'watching sick people'-the clinic setting as a factor in the experiences of gay men participating in AIDS clinical trialls. AIDS Care 1995;**7 (2)**:147-58.

200. Feathersone K, Donovan JL. Random allocation or allocation at random? Patients' perspective of participation in a randomised controlled trial. BMJ 1998;**317**:1177-80.

201. Blair C, Kacser E, Porteous D. Gene therapy for cystic fibrosis: a psychosocial study of trial participants. Gene Ther 1998;**5**:218-22.

202. Harrison J. clinical trials: a patient's view. MRC News 1998;**Autumn**:22-3.

203. Oakley A. Who's afraid of the randomized controlled trial? Some dilemmas of the scientific method and "good" research practice. Women and Health 1989;**15(4)**:25-59.

204. Silverman WA. Patient's preferences and randomised trials. Lancet 1994;**343**:1586.

205. Health Services Research Group. Studying patients' preferences in health care decision making. Can Med Assoc J 1992;**147(6)**:859-64.

206. Jack WJL, Chetty U, Rodger A. Recruitment to a prospective breast conservation trial: Why are so few patients randomised? BMJ 1990;**301**:83-5.

207. Rimer BK, Schildkraut JM, Lerman C, Lin TH, Audrain J. Participation in a women's breast cancer risk counseling trial. Who participates? Who declines? High Risk Breast Cancer Consortium. Cancer Suppl 1996;**77**:2348-55.

208. Fallowfield LJ, Hall A, Maguire GP, Baum M. Psychological outcomes of different treatment policies in women with early breast cancer outside a clinical trial. BMJ 1990;**301**:575-80.

209. Tercyak KP, Johnson SB, Kirkpatrick KA, Silverstein JH. Offering a randomized trial of intensive therapy for IDDM to adolescents. Diabetes Care 1998;**21 (2)**:213-5.

210. Criqui MH, Barrett-Connor E, Austin M. Differences between respondents and non-respondents in a population-based cardiovascular disease study. Am J Epidemiol 1978;**108**:367-72.

211. Riordan FA, Thomson APJ. How to get patients' consent to enter clinical trials [letter]. BMJ 1996;**312**:185-6.

212. Miller C, Searight HR, Grable D, Schwartz R, Sowell C, Barbarash RA. Comprehension and recall of the informational content of the informed consent document: an evaluation of 168 patients in a controlled clinical trial. J Clin Res Drug Dev 1994;**8**:237-48.

213. Harrison K, Vlahov D, Jones K, Charron K, Clements ML. Medical eligibility, comprehension of the consent process, and retention of injection drug users recruited for an HIV vaccine trial. J Acquir Immune Defic Syndr Hum Retrovirol 1995;**10,No.3**:386-90.

214. Oddens BJ, Algra A, Van Gijn EJ. How much information is retained by participants in clinical trials? Nederlands Tijdschrift Voor Geneeskunde 1992;**136**:2272-6.

215. Dal-Re R. Clinical research with drugs: a study of the influence of information about adverse reactions on obtaining informed consent. Med Clin (Barc) 1991;**96**:566-9.

216. Ubel PA, Merz JF, Shea J, Asch DA. How preliminary data affect people's stated willingness to enter a hypothetical randomized controlled trial. J Invest Med 1997;**45(9)**:561-6.

217. Postlethwaite RJ, Reynolds JM, Wood AJ, Evans JHC, Lewis MA, Eminson DM. Recruiting patients to clinical trials: lessons from studies of growth hormone treatment in renal failure. Arch Dis Child 1995;**73**:30-5.

218. Mason S, Brown J, Levene M. What is this thing called "randomise"? [letter]. Lancet 1996;**350**:1416.

219. Morse JM. Designing funded qualitative research. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. London: Sage Publications, 1994:220-35.

220. Donovan JL et al. The CLasP Study: Three linked pragmatic randomised controlled trials to assess the effectiveness and cost-effectiveness of treatments for benign prostatic disease. Final Report to the South and West and Northern Research and Development Directories.

221. Donovan JL, Peters TJ, Neal DE, Brookes ST, Gujral S, Chacko KN, et al. A randomised trial comparing transurethral resection of the prostate, laser therapy and conservative management in men with symptoms associated with benign prostatic enlargement: the CLasP study. J Urol 2000;**164**:in press.

222. Silverman D. Qualitative methodology and sociology. Aldershot, England: Gower Publishing Company Limited, 1985.

223. Denzin NK, Lincoln YS, editors. Handbook of Qualitative Research. London: Sage Publications, 1994.

224. Addison RB. Grounded hermeneutic research. In: Crabtree BF, Miller WL, editors. Doing qualitative research. London: Sage Publications, 1992:110-24.

225. Hughes J. The Philosophy of Social Reserch. London: Longman, 1990.

226. Shils EA, Finch HA, editors. Max Waber on the Methodology of the Social Sciences. Glencoe,US: The Free Press, 1949.

227. Hammersley M, Atkinson P. Ethnography. Principles in practice. 2nd ed. London: Routledge, 1995.

228. Schutz A. The phenomenology of the social world. London: Northwestern University Press, 1967.

229. Blumer H. Symbolic interactionism: perspective and method. Englewood Cliffs,NJ: Prentice Hall, 1969.

230. Schwandt TA. Constructivist, interpretivist approaches to human enquiry. In: Denzin NK, Lincoln YS, editors. Handbook of Qualitative Research. London: Sage Publications, 1994:118-37.

231. Hammersley M. Herbert Blumer and qualitative method. Qualitative Studies Education 1990;**3(1)**:31-6.

232. Joas H. Symbolic Interactionism. In: Giddens A, Turner JH, editors. Social Theory Today. Oxford: Basil Blackwell Ltd, 1987:82-115.

233. Denzin NK. Symbolic interactionism and cultural studies. Cambridge: Basil Blackwell, 1992.

234. Glaser BG, Strauss AL. The Discovery of Grounded Theory. Chicago: Aldine Publishing Company, 1967.

235. Strauss A, Corbin J. Grounded theory methodology: an overview. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. London: Sage Publications, 1994:273-85.

236. Strauss A, Corbin J. Basics of qualitative research: grounded theory procedures and techniques. London: Sage Publications, 1990.

237. Glaser B. Theoretical sensitivity. Mill Valley,CA: Sociological Press, 1978.

238. Burgess RG. The unstructured interview as a conversation. In: Burgess RG, editor. Field research: a source book and field manual. London: Routledge, 1982:107-10.

239. Mays N, Pope C. Qualitative research in health care. London: BMJ Publishing Group, 1996.

240. Britten N. Qualitative interviews in medical research. BMJ 1995;**311**:251-3.

241. Kirk J, Miller ML. Reliability and validity in qualitative research. London: Sage Publications, 1986.

242. Dingwall R. Accounts, interviews and observations. In: Miller G, Dingwall R, editors. Context and method in qualitative research. London: Sage Publications, 1997:51-65.

243. Collins P. Negotiating selves: reflections on 'unstructured' interviewing. Sociological Research Online 1998;**3(3)**:1-14.

244. Silverman D. The logics of qualitative research. In: Miller G, Dingwall R, editors. Context and method in qualitative research. London: Sage Publications Ltd, 1997:12-25.

245. Kuzel AJ. Sampling in qualitative inquiry. In: Crabtree BF, Miller WL, editors. Doing qualitative research. London: Sage Publications, 1992:31-44.

246. Patton MQ. Qualitative evaluation and research methods. 2nd ed. Newbury Park,CA: Sage, 1990.

247. Mays N, Pope C. Rigour and qualitative research. BMJ 1995;**311**:109-12.

248. Punch M. Politics and Ethics in Qualitative Research. In: Denzin NK, Lincoln YS, editors. Handbook of Qualitative Research. London: Sage Publications, 1994:83-97.

249. Fontana A, Frey JH. Interviewing: the art of science. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. London: Sage Publications, 1994:361-76.

250. Miles MB, Huberman EM. Qualitative Data Analysis. 2nd ed. London: Sage, 1994.

251. Burnard P. Searching for meaning: a method of analysing interview transcripts with a personal computer. Nurse Educaton Today 1994;**14**:111-7.

252. Reid AO. Computer management strategies for text data. In: Crabtree BF, Miller WL, editors. Doing qualitative research. London: Sage Publications, 1992:125-45.

253. Cobb AK, Hagemaster JN. Ten criteria for evaluating qualitative research proposals. Journal of Nursing Education 1987;**26(4)**:138-42.

254. BSA Medical Sociology Group Committee. Criteria for the evaluation of qualitative research papers. BSA Medical Sociology Group.

255. Hammersley M. What's wrong with ethnography? London: Routledge, 1992.

256. Silverman D. Interpreting qualitative data. Methods for analysing talk, text and interaction. London: Sage Publications, 1993.

257. Janesick VJ. The dance of qualitative research design: metaphor, methodolatry, and meaning. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. London: Sage Publications, 1994:209-19.

258. Wolcott HF. On seeking and rejecting validity in qualitative research. In: Eisner EW, Peshkin A, editors. Qualitative inquiry in education: the continuing debate. New York: Teachers College Press, 1990:121-52.

259. Donmoyer R. Generalizability and the single case study. In: Eisner EW, Peshkin A, editors. Qualitative inquiry in education:the continuing debate. New York: Teachers College Press, 1990:175-200.

260. Lincoln YS, Guba EG. Naturalistic Enquiry. Beverley Hills,CA: Sage, 1985.

261. Bloor M. Techniques of validation in qualitative research: a critical commentary. In: Miller G, Dingwall R, editors. Context and method in qualitative research. London: Sage Publications Ltd, 1997:37-50.

262. Miles MB, Huberman AM. Qualitative data analysis. 2nd ed. London: Sage Publications, 1994.

263. Huberman AM, Miles MB. Data management and analysis methods. In: Denzin N, Lincoln YS, editors. Handbook of qualitative methods. London: Sage Publications, 1994:428-44.

264. Silverman D. Applying the qualitative method to clinical care. In: Daly J, MacDonald I, Willis E, editors. Researching health care: designs, dilemmas, disciplines. London: Tavistock/Routledge, 1992:176-88.

265. Dingwall R. 'Dont mind him- he's from Barcelona'. In: Daly J, MacDonald I, Willis E, editors. Researching health care: designs, dilemmas, disciplines. London: Tavistock/Routledge, 1992:161-75.

266. Olesen V. Feminism and models of qualitative research. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. London: Sage Publications, 1994:158-74.

267. Allen RE, editor. The Concise Oxford Dictionary of Current English. Eigth ed. Oxford: Oxford University Press, 1990.

268. Jorgenson J. Co-constructing the interviewer/co-constructing 'family'. In: Steier F, editor. Research and Reflexivity. London: Sage Publications Ltd, 1991:210-25.

269. Dingwall R. Ethics and ethnography. Sociological Review 1980;**28(4)**:871-91.

270. Hammersley M, Atkinson P. Ethnography: Principles in practice. London: Tavistock, 1983.

271. Becker G. Disrupted lives. Berkley: University of California Press, 1997.

272. Oakley A. Social support and motherhood. Oxford: Blackwell, 1996.